New C-C and C-N bond forming reactions mediated by chromium complexation

Graham, Alan

Award date:
1996

Awarding institution:
University of Bath

NEW C-C AND C-N BOND FORMING REACTIONS MEDIATED BY

CHROMIUM COMPLEXATION.

Submitted by

Alan Graham

for the degree of Ph.D.

of the University of Bath

1996

COPYRIGHT

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Contents

Copyright		***i***
Dedication		***ii***
Acknowledgements		***iv***
Abbreviations		***v***

Chapter 1	**Introduction**		*Pg.*
	Abstract	**1.1**	*1*
	Introduction	**1.1.1**	*4*
	Baldwin's rules for ring closure	**1.2**	*6*
	The organic chemistry of chromium	**1.3.1**	*9*
	Preparation	**1.3.2**	*11*
	Stereoselectivlty in preparation	1.3.2.1	*14*
	Decomplexation	1.3.2.2	*17*
	Reactions of chromium complexes		
	Replacement of halogens	**1.4.1**	*18*
	Cross coulping reactions	1.4.1.1	*22*
	Replacement of Oxygen	1.4.2	*23*
	Replacement of hydrogen	1.4.3	*25*
	Intramolecular replacement of hydrogen	1.4.3.1	*30*

Double addition/de-aromatisation		**1.5**	*32*
	Protons as the electrophile	1.5.1	*33*
	Carbon as the electrophile	1.5.2	*35*
Generation and use of metal stabilised ions		**1.6**	*37*
	Arene deprotonation	1.6.1	*37*
	Benzylic deprotonation	1.6.2	*39*
	Benzylic cations	1.6.3	*41*
Reactions external to the aromatic π system		**1.7.1**	*44*
	Addition and electrophilic quenching	1.7.2	*47*

Chapter 2 **Synthesis, results and discussion**

6-endo-trig cyclisation	**2.1**	*50*
5-exo-trig spirocyclisation	**2.2**	*59*
6-exo trig spirocyclisation	**2.3**	*73*
6-exo-trig cyclisation	**2.4**	*83*
Conclusions	2.4.1	*93*

Chapter 3 **Experimental**

Instruments and experimental techniques	**3.1.1**	*95*
General	3.1.2	*95*
Analysis and spectroscopy	3.1.3	*95*
Solvents and reagents	3.1.4	*96*
Chromatography	3.1.5	*96*
Experimental	**3.2**	*99*
References	**3.3**	*133*

Chapter 4 **Appendices**

X -Ray analysis of compound (86)	***i***
X -Ray analysis of compound (87)	***ii***
^{13}C, ^{1}H, 2D, NOESY and COSEY spectra data for selected compounds	***iii***

Dedicated to Kristin and Louis

Para mi solo recorrer los caminos que tienen corazon, cualquier camino que tenga corazon. Por ahi yo recorro, y la unica prueba que vale es atravesar todo su largo. Y por ahi yo recorro mirando, mirando, sin aliento.

Don Juan Matus (unknown)

We live together, we act on, and react to, one another; but always and in all circumstances we are by ourselves. The martyrs go hand in hand into the arena; they are crucified alone.

Aldous Huxley (1894 - 1963)

ACKNOWLEDGEMENTS

The work described in this thesis was carried out in the Organic Chemistry Department of the University of Bath, between February 1992 and December 1995. Also a large portion of the early work was carried out in the Medicinal Chemistry Department of Glaxo Group Research, Ware, between January and March 1993.

I am deeply indebted and grateful to Professor Malcom Sainsbury, my supervisor at Bath, for his help, guidance and support. Also the help and advice from Glaxo Group Research, especially Dr. Mark Ladlow and Dr. Alan Naylor.

My appreciation goes to the technical staff at the University of Bath for their invaluable services. I would like to thank Mr. John Bradley and Mr. Russel Barlow (organic stores), Mr. Dave Wood and Mr. Harry Hartnell (NMR spectroscopy), Mr Chris Cryer (mass spectrometry), Mr. Alan Carver (elemental microanalysis), and for their invaluable contribution of X-ray crystallography, Dr. Mary Mahon and Dr. Kieran Molloy.

Finally, I would like to thank my friends and colleagues. Kristin Alsop, Matt Sage, Chris Lacy, Derradji Boumrah, Max Liu, Simon Diston, Matt Fletcher, Cida Kawamoto, Gwo-sen Lin, Anne Hackett, Neil Smith, Kevin Williams, Prashant Verma, Philip Podmore, Chris Howarth and Etty Abergel.

To all of you, it has always been a pleasure and will always remain one. My thanks and I wish you all the best.

Alan Graham Feb 1996

ABBREVIATIONS

Ac	-	Acetyl
Amberlyst-15/H^+	-	Strongly acidic, macromolecular resin
b.p.	-	Boiling point
BSA	-	Bis(trimethylsilyl)acetamide
C.I.	-	Chemical ionisation
18-Crown-6	-	1,4,7,10,13,16-Hexaoxocycloctadecane
$BF_3.OEt_2$	-	Borontrifluoride etherate
2D-COSY	-	Two dimensional correlated spectroscopy
Cyclhex	-	Cyclohexane
DBU	-	1.8-Diazabicyclo[5.4.0]undec 7-ene
δ_c	-	Chemical shift in ppm down field of TMS
DCC	-	Dicyclohexylcarbodiimide
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
d.e.	-	Diameric excess
DEA	-	Dichloromethane:Ethanol: 880-Ammonia
DEAD	-	Diethyl azodicarboxylate

90 or 135-DEPT	-	90 or 135 distortionless enhancement by polarisation transfer
δ_h	-	Chemical shift in ppm down field of TMS
DMAP	-	N,N-Dimethyl-4-aminopyridine
DMF	-	Dimethyl formamide
DMPU	-	N,N'-Dimethyl-N,N'- urea (1,3-Dimethyl-2-oxo-hexahydropyrimidine)
DMSO	-	Dimethyl sulfoxide
DNBE	-	Di-n-butyl ether
e.e.	-	Enantiomeric excess
E.I.	-	Electron ionisation
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
h	-	Hour
Hex	-	Petrol ether (b.p. 60-80°C) (predominately Hexane)
HMDS	-	Hexamethyldisilazane
HMPA	-	Hexamethylphosphoramide
HOMO	-	Highest occupied molecular orbital
Hz	-	Hertz (s^{-1})
J	-	Coupling constant in Hz
LAH	-	Lithium aluminium hydride

LDA	-	Lithium diisopropylamide
2,6-Lutidine	-	2,6-Dimethylpyridine
L.U.M.O.	-	Lowest un-occupied molecular orbital
*m*CPBA	-	*m*-Chloro-perbenzoic acid
Me	-	Methyl
mp.	-	Melting point
Ms	-	Methanesulphonyl (mesyl)
M.O.	-	Molecular orbital
NMR	-	Nuclear magnetic resonance
n.O.e	-	Nuclear overhauser effect spectroscopy
2D-NOESY	-	Two dimensional n.O.e spectroscopy
Ph	-	Phenyl
PPh_3	-	Triphenylphosphine
ppm	-	Parts per million
Pth	-	Phthalimide
R_f	-	Retention factor
R.T.	-	Room temperature
S_N1	-	Substitution nucleophilic unimolecular
S_N2	-	Substitution nucleophilic bimolecular
S_NAr	-	Substitution nucleophilic at an arene centre
TBDMS	-	Tertiarybutyldimethylsilyl
TFAA	-	Trifluoroacetic anhydride

TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
Tlc.	-	Thin layer chromatography
TMS	-	Trimethylsilane
TMEDA	-	Tetramethylethylene-diamine
		acetic acid
Tol	-	Toluene
Trf	-	Triflate (SO_2CF_3)
p-TSA	-	*p*-Toluenesulphonyl

Chapter 1

Introduction

Abstract

(1.1)

It is known that the complexation of a styrene to chromium tricarbonyl mediates a novel C-N bond forming reaction. This is surveyed in section 1.1 '.

The aim of this project was to study the scope of this type of reaction '. In the process several novel compounds were synthesised using methodology involving both new and established chemical methods.

Starting with the mobile styrene derivative (23) [compared to the rigid structure in compound (2)] which was anticipated to give access to the 6,6,6 ring system shown on page (3), we progressed to the preparation of the spirocyclic precursors (53), (62), (65), (75), (76) and (77). These compounds were expected to give entry to an important class of spirocyclic alkaloids. The creation of a new route to such compounds incorporating control would have wide applicability, however, none of the precursors cyclised as required. These failures in reactivity caused a redirection of research the synthesis of a compound bearing as much resemblance to the product of the only known successful ring closure of this type '. Thus compound (92), shown on the page (3), became our last synthetic target.

Cyclisation of compound (92) also failed which unfortunately means that the scope of this potentially useful reaction remains unfulfilled.

In conclusion, several interesting new compounds have been prepared and converted into chromium complexes but the primary objectives of the research were not attained. Possible reasons for this failure are analysed.

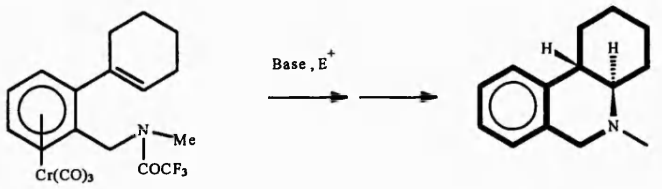
This thesis is sub-divided into four chapters:

Chapter 1: **Introduction**.

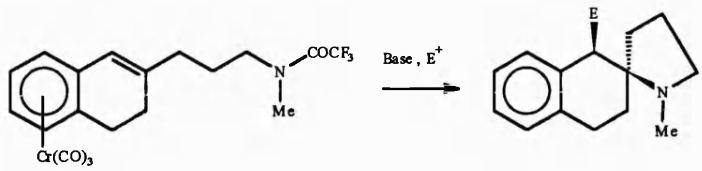
Chapter 2: **Synthesis, results and discussion**.

Chapter 3: **Experimental**

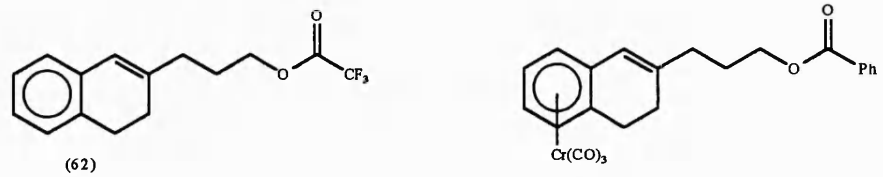
Chapter 4: **Appendices**: *X -Ray analysis of compounds (86) and (87) and selected spectral data.*



(23) The 6,6,6 fused ring system

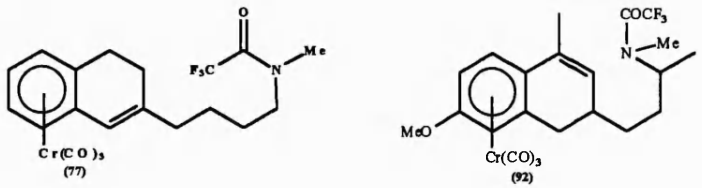


(53) (54)



(62) (65)

(75) (76)



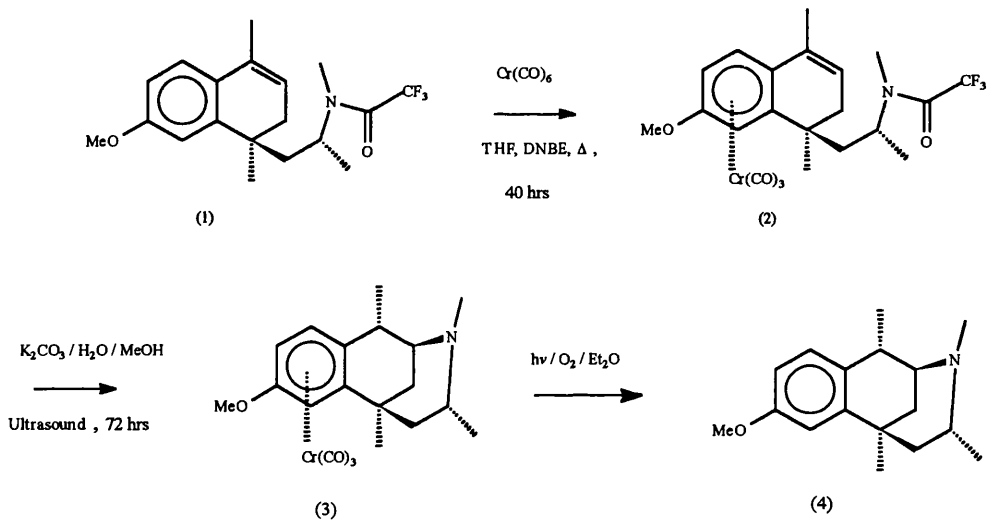
(77) (92)

Intermediates synthesised for study

INTRODUCTION

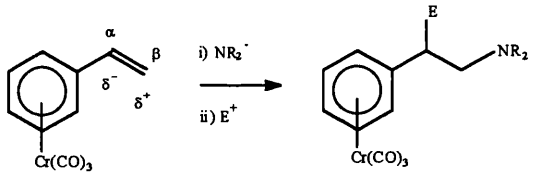
(1.1.1) ***Previous work:***

It has recently been shown that chromium tricarbonyl complexation of the electron rich arene (1) yields (2) and treatment of this product with aqueous base gives the cyclisation product (3). When decomplexed, this compound gives the final product (4)[1]. It has been shown that without the chromium tricarbonyl unit compound (1) does not cyclise to (4). Thus proving that the chromium tricarbonyl unit can be an essential mediator for novel C-N and C-H bond forming reactions [scheme 1].



Scheme 1

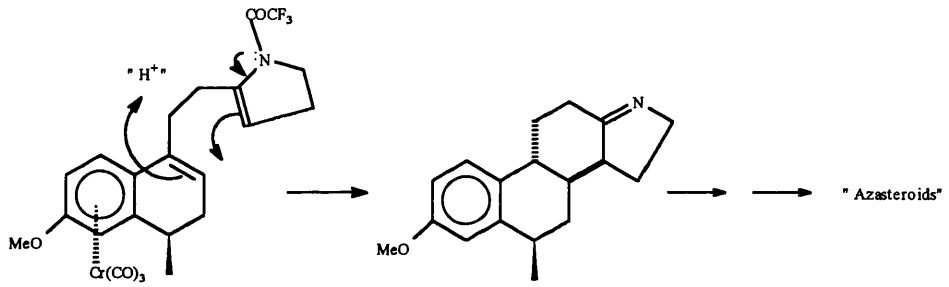
The above process was the first example of intramolecular Carbon - Nitrogen bond formation promoted by chromium complexation [many examples of Carbon - Carbon bond formation have been reported (see chapter 1)], and indicated possibilities for other C-N bond formations at the β-position of styrenes with concomitant electrophile quenching at the α-position [scheme 2]. To this there is the added possibility of facial selectivity, due to the size of the metal tripod, and where appropiate chirality induction as indicated in scheme 1.



Scheme 2

'The formal polarization of the chromium styrene unit'

Of the many possibilities open for the study of intramolecular cyclisations based on this methology, coupling reactions of various tethered nitrogen nucleophiles, or enamines [where reaction through C-3 would be envisaged] to complexed styrenes would give access to a variety of synthetically and chemically useful compounds such as azasteroids [scheme 3].



Scheme 3

Thus, further study of this type of methology was deemed necessary to establish the scope and limitations of the approach and this is where this project began.

(1.2.) Baldwin's rules for ring closure.

J.E. Baldwin developed a set of useful guidelines to predict favourable cyclisation processes. These were based on empirical observations of a variety of organic ring closure reactions catalogued in the chemistry literature [2,3,4]. These (rules) are drawn from the physical requirements of the various transition states involved and other stereo-electronic effects predicted elsewhere [5].

Three main classes of reactions were considered :

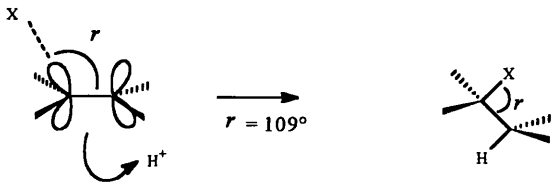
Additions to tetrahedral carbon atoms bearing a leaving group,

(given the **Tet.** Suffix, which relates to sp^3 centres).

Additions to double bonds, (given the **Trig.** suffix, relating to sp^2 centres), and

Additions to triple bonds, (given the **Dig.** suffix, relating to sp centres).

Additions to trigonal systems (**Trig**) require that the nucleophile approaches the double bond in the same plane as the electron cloud of the π^*–bond, i.e. perpendicular to the plane of the atoms that make up the planar unit, and at a predicted angle, *r*, of approximately 109° w.r.t. the basal plane (see below).



Addition to the Trigonal System.

In order to fully define the possible reactions more suffixes are necessary :

One describes the resulting ring size (inclusive of any hetero atoms) i.e. 6- for a piperidine ring, and another the position of the breaking bond in relation to the smallest ring so formed:

Exo when it is outside the ring and

Endo when it is inside the ring.

The terms **"Favoured"** or **"Disfavoured"** are then applied to signify whether in the absence of other factors the cyclisations are likely to proceed or not. Obviously the relative sizes of the atomic radii and use of appropriate atomic orbitals are important as the rules are intended to cover only the first row elements. This being said they do have some validity for the heavier elements.

The resulting **"Rules"** are outlined below.

Rule 1 : Tetrahedral Systems:

(a) 3 to 7-**Exo-Tet** are all **Favoured** processes with many known examples;

(b) 5 to 6-**Endo-Tet** are **Disfavoured.**

Rule 2 : Trigonal Systems:

(a) 3 to 7-**Exo-Trig** are all **Favoured** processes with many known examples;

(b) 3 to 5-**Endo-Trig** are **Disfavoured** ; 6 to 7-**Endo-Trig** are **Favoured.**

Rule 3 : Digonal Systems:

(a) 3 to 4-**Exo-Dig** are **Disfavoured** processes; 5 to 7-**Exo-Dig** are **Favoured.**

(b) 3 to 7-**Endo-Dig** are **Favoured.**

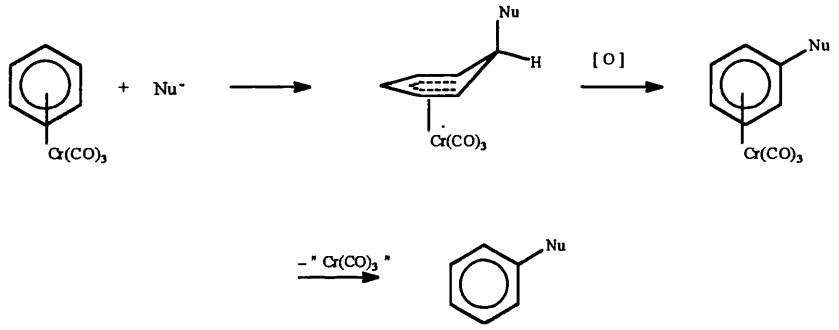
It should be stated that there are notable exceptions to the "rules" which were never intended to be dogmatic - even though many authors who had difficulty in explaining cyclisation reactions "before" Baldwin now find excuses to criticise them.

These rules are included here for completeness as the terms and suffixes are used throughout this work and for general information as knowledge of them are of use in all areas of chemistry.

THE ORGANOMETALLIC CHEMISTRY OF CHROMIUM.

(1.3.1) *Background*

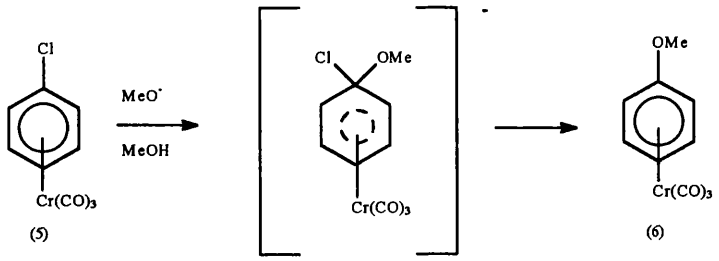
The first η^6-arene-transition metal complexes were prepared in the 1950's [6,7]. It was recognised that the electron withdrawing properties of the metal generated complexes that undergo nucleophile additions. Nucleophilic addition gives cyclohexadienyl complexes but these may rearrange to afford new arene complexes and, after decomplexation, substituted arenes [scheme 4].



Scheme 4

An example is the conversion of the haloarene complex (5) [scheme 5] through *ipso*-substitution into the anisole complex (6). This is directly comparable with a classical S_NAr substitution reaction and thus the $Cr(CO)_3$ unit is similar to the effect of a 4-nitro substituent in the reactions of haloarenes with methoxide ion in methanol [8]. In the case of the haloarene complexes the reactivity of haloarene ligands towards methoxide decreases through the series: fluorobenzene > chlorobenzene > chlorotoluene [9]. The rate of reaction with any other halogen is too slow to be of any synthetic use.

Both procedures generate Meisenheimer type complexes that are isolable in the case of carbon and other non equilibrating nucleophiles, these then need to be treated with an oxidising agent to regenerate the aromatic nucleus and the final product [scheme 5] [10].



Scheme 5

An ***ipso*** - Substitution

In general the complexation of an arene to a metal increases the acidity of the aromatic protons much more markedly than the benzylic protons, when present. Note, however that in toluenes the benzylic protons are much more acidic than those of the nucleus to start with and, although complexation has an unequal effect on the two types, it is still α-deprotonation which occurs first in the organometallic derivatives, unless special conditions are selected.

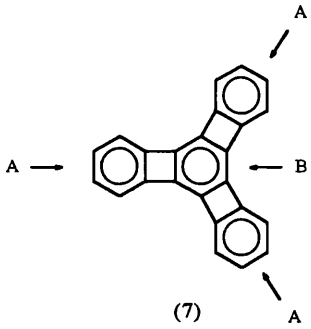
The majority of work in this area has been directed towards chromium arenes but it must be noted that manganese and iron species are very important. The preference for chromium is due to the ease of complexation, but this is no longer a limitation [11, 12].

(1.3.2) **PREPARATION**

The most general and widely used method for the preparation of an (η^6-arene)$Cr(CO)_3$ complex is the thermally-promoted exchange from hexacarbonylchromium (commercially available) and the arene. The main problem with this method is that sublimation of the chromium hexacarbonyl onto the condenser wall tends to occur. Fortunately this can quite easily be overcome by using THF:DNBE (ca 1:12) as the solvent system. In this, THF washes the solid sublimation product back into the reaction but, even though this is effective, a careful eye needs to be kept on the reaction throughout. Sometimes mechanical intervention by the experimentalist, to chip the solid away, is required.

This method is known as the Mahaffy-Pauson procedure [13] but it may be complicated by low yields due to thermal degradation of the required complex over the long reaction times and high temperature needed (ca 10-24 hrs and 130-170°C). Some of the problems associated with this method have been overcome by the use of small amounts of organic additives [14] and the use of alternative solvents, i.e. 1-3 mol% BuOAc in boiling decalin.

Where almost total facial selectivity during complexation is possible, such as compound (1) [scheme 1] [15], this advantage may be compromised by thermally induced equilibration from the kinetic to the thermodynamic isomer. A good example of this is the selective complexation of (7) (next page) which has two distinct regioisomers (X and Y). These correspond to the kinetic and thermodynamic products respectively. Thermally induced complexation in dioxane at 80°C for 14 hrs gives the thermodynamic *exo*-isomer (Y) where as complexation using a ligand exchange reaction with naphthalenechromium tricarbonyl in THF at 50°C gives the kinetic *endo*-isomer (X) [16]. The *endo*-isomer is regarded as the more nucleophilic of the two possibilities [see diagram on the next page].



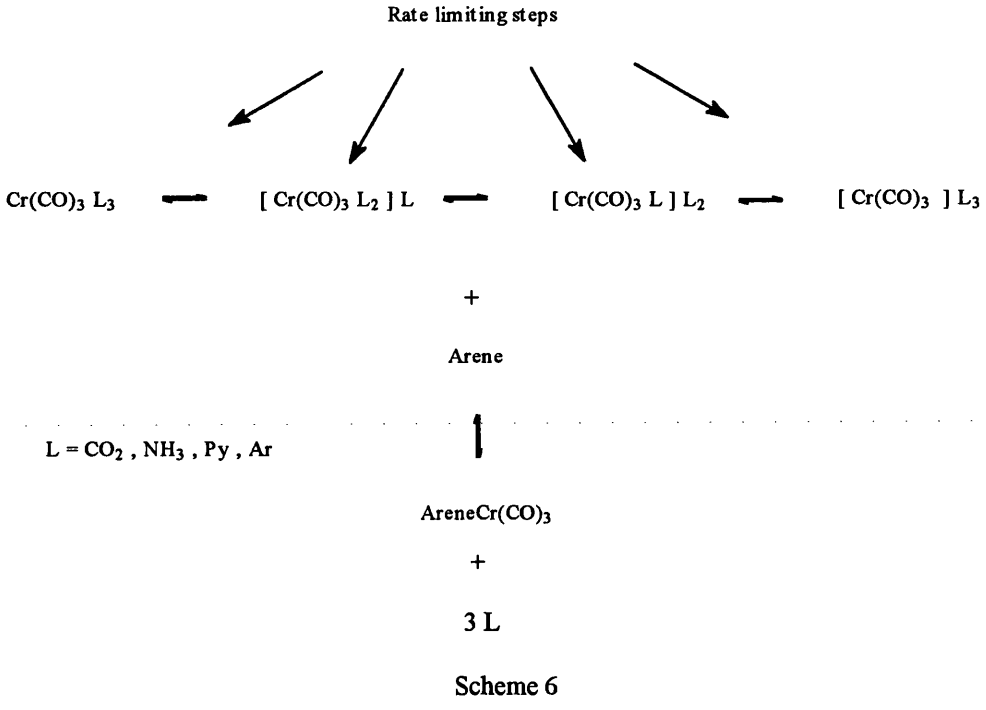
(7)

A = *Exo* ring (Thermodynamically most stable) Giving isomer Y

B = *Endo* ring (Kinetically favoured/most nucleophilic) Giving isomer X

The previous example illustrates an important point about the chromium tricarbonyl unit which is it's mobility under appropriate conditions [16]. In this case the measured free energy for the interchange between X and Y is $\Delta H = 115$ kJ mol^{-1}. Further study upon the compounds in the example produced a value for the rotation about the η-bond to be $\Delta H = 46.4$ KJ mol^{-1} confirming the assumptions that the arrangement of the carbon monoxide ligands at 120^{o} to each other exist in non-equivalent conformers [16].

In complexations where arene + $Cr(CO)_3L_3$ gives the arene-$Cr(CO)_3$ plus 3L [scheme 6], the rate limiting step appears to be the initial dissociation of the ligand (L) from the reagent. The use of ligands that are weakly bound, such as pyridine or ammonia, make the rate limiting step a less demanding process, promoting easier generation of the coordinatively unsaturated species that is responsible for the complexation. It is interesting to note that this coordinatively unsaturated chromium species is also the one desired for catalytic activity [17]. Promotion of dissociation can be further improved by the addition of Lewis acids or weak donor ligands such as α-picoline [18] or THF [19]. In the case of Lewis acids the use of pyridine as a ligand and boron trifluoride etherate in boiling ether gives a mild and effective complexation reaction and permits the possibility of recycling the chromium [20].



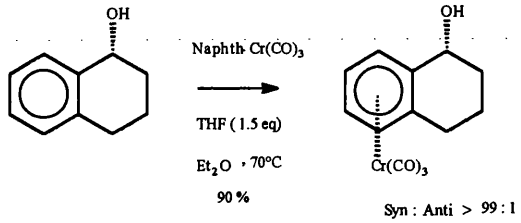
Scheme 6

The use of the commercially available naphthaleneCr(CO)$_3$ is now one of the most effective reagents for generation of the arene-metal complexes. The great reactivity of this reagent and the low temperature of reaction, allows the selective preparation of kinetic, rather than the thermodynamic, regioisomer [21].

Photolytically-promoted generation of (arene)Cr(CO)$_3$ is carried out under milder conditions than thermally promoted reactions and has been exploited for the preparation of otherwise difficult to obtain complexes such as benzo[3,4-c]thiophenechromium tricarbonyl [22]. Normally this complex is unstable under thermal conditions [23].

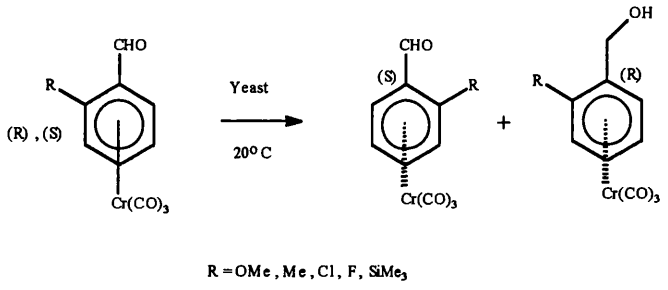
(1.3.2.1) STEREOSELECTIVITY IN COMPLEXATION

A wide variety of enantio-rich areneCr(CO)$_3$ complexes have been synthesised to date by several methods. Common is the use of naphthaleneCr(CO)$_3$ as an exchange ligand. With enantiopure or enriched substrates with a stereogenic centre at the benzylic site high diastereoselectivity is obtained [24] in the resulting complex. Also, with enantiopure substrates containing alcohols in the benzylic position *syn*-facial transfer of the metal is mediated by the Lewis base character of the alcohol. This preference has been known for several years [25] [scheme 7].



Scheme 7

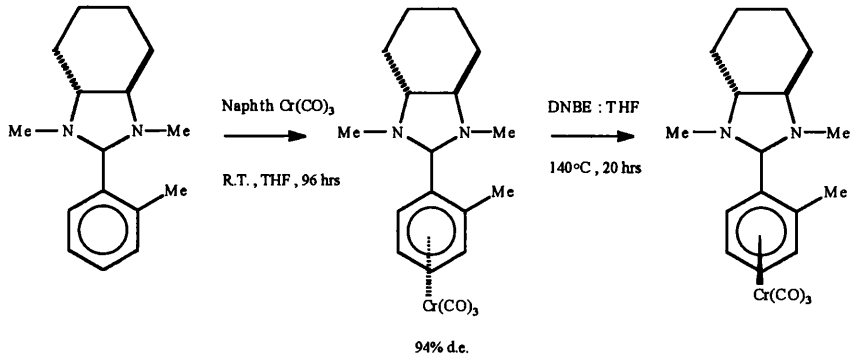
Enzymatic resolution of a racemic complex is possible. For example aldehyde complexes can be selectively reduced with commercial baker's yeast giving a benzylic alcohol with good to high e.e. [scheme 8] [26].



Scheme 8

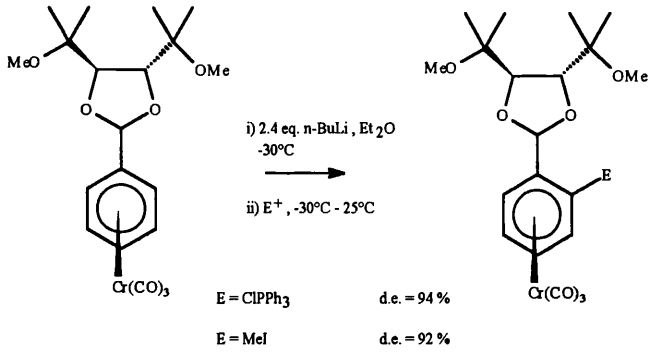
There are other examples of related enzymatic resolutions, but they are rather specific and limited in usage and it is much more valuable to induce asymmetry at an early stage in the reaction.

Direct asymmetric introduction of the $Cr(CO)_3$ moiety onto a 1,2-disubstituted arene ring has been achieved; for example the aminal derived from (R,R)-1,2-bis(N-methylamino)cyclohexane and *o*-tolualdehyde is very efficient in directing the highly stereoselective transfer of $Cr(CO)_3$ from the η^6-naphthalene complex at room temperature. Here it is interesting to note again the ability of the metal to equilibrate under thermal conditions to give the thermodynamic isomer [27] [scheme 9].



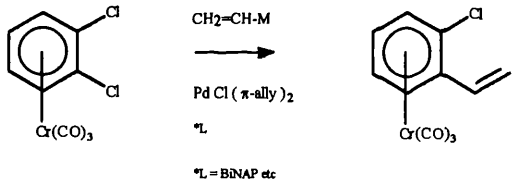
Scheme 9

Chiral centres attached to the arene complex have thus been used in two ways to bring about remote optical enrichment [schemes 7 + 9]. In addition, there are many examples of selective deprotonation of either a pro R or a pro S aromatic hydrogen and the derived anion then quenched with an electrophile to give enantio enriched products. Scheme 10 shows a good example [28].



Scheme 10

Finally recent work by Uemura has shown that the meso (η^6-1,2-dichlorobenzene)$Cr(CO)_3$ complex, when treated with an optically active Pd(0) catalyst and a vinylborane reagent, resulted in selective reaction of one of the enantiotropic C-Cl bonds. Although the selectivity is not high it is none the less significant and opens up hope for new methodology based upon chirality induction from common, chiral reagents such as BINAP, DIOP or CHIRAPHOS [27] [scheme 11].



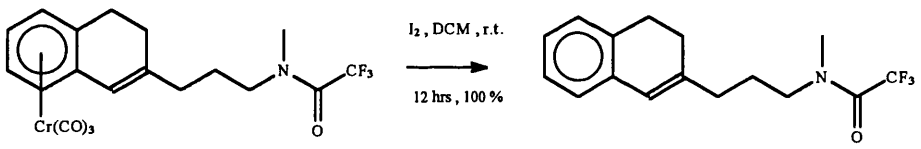
Scheme 11

(1.3.2.2) **DECOMPLEXATION**

AreneCr(CO)$_3$ complexes in solution are normally unstable to light (including that from artificial sources) and air, which is why all solvents require de-gassing before use. Once the complexes are in the solid state however, they are relatively stable and decompose only slowly over time (days). Decomplexation can be effected by contact with oxidising agents, even very mild ones such as iodine [29]. This can also often be achieved through exposure of an ethereal solution of the complex to air in the presence of natural light [30]. Decomplexation then takes place in a matter of hours.

As mentioned earlier, the addition of pyridine [20] to the arene complex under reflux for 2 hrs will free the arene ligand and then generate a (Py)$_3$Cr(CO)$_3$ compound as a by-product that can later be used to form new arene complexes in the presence of boron trifluoride etherate. However in most cases the decomplexation gives rise to the free arene, carbon monoxide, chromium(III) species and the reduced oxidant. For one off syntheses the chromium is discarded and it is only in cases where oxidation is not used and ligand replacement is that the possiblity for recycling of the metal becomes an option [20].

Although all of these methods have been used and are still of use, the most widely employed are the exposure to air and light or iodine [scheme 12]. Unfortunately the exposure to iodine may also cause oxidation of the organic component (for examples see later).



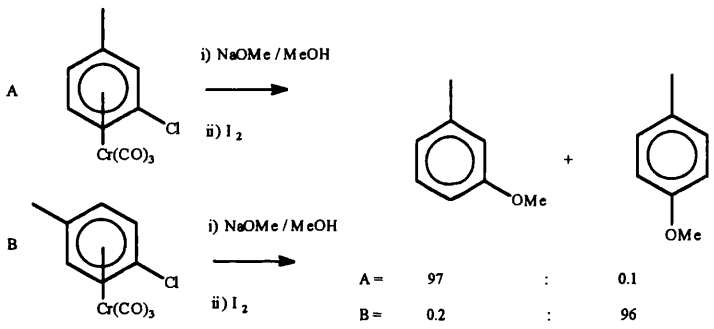
(53) (52)

Scheme 12

REACTIONS OF ARENE $Cr(CO)_3$ COMPLEXES

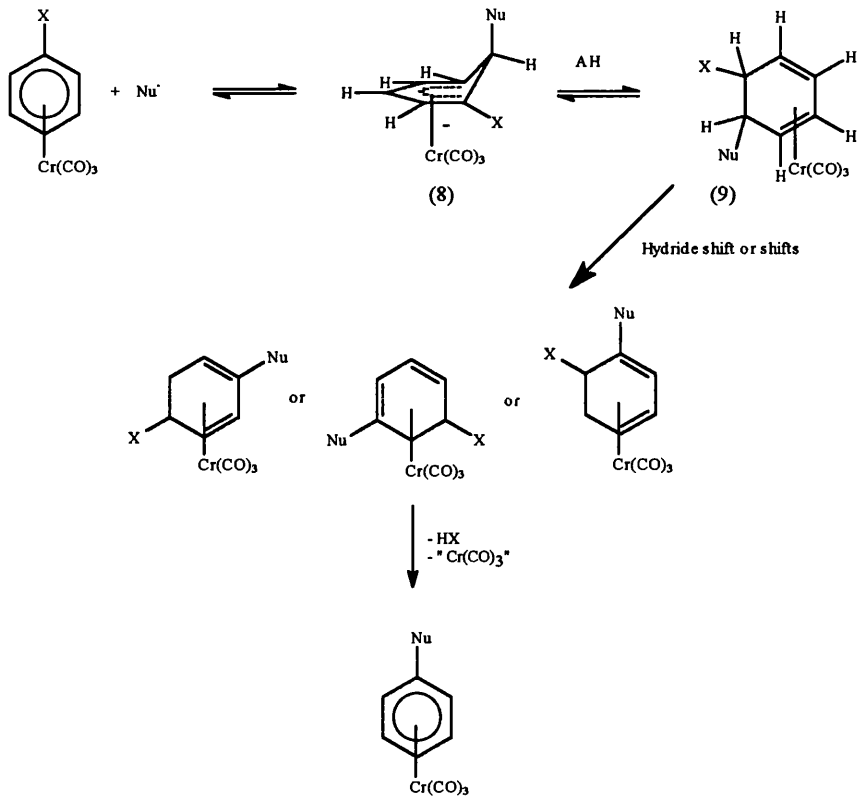
(1.4.1) *S_NAr REPLACEMENT OF HALOGENS.*

Intermolecular replacement of halogens by carbon and heteroatom nucleophiles is one of the major areas in which chromium complexation is valuable. As mentioned earlier, only the displacement of fluoride or chloride ions is practical and so although bromo and iodo complexes are known, they are of no use in synthesis [31]. Fluoride replacement is 2000 times faster than chloride, a fact as evidence that the rate limiting step is the addition of the nucleophile. Fast loss of halide then occurs [32]. This conclusion may not be universally true since there are some contradicting results using nitrogen based nucleophiles [33].



Scheme 13

Intermolecular reactions such as that shown in scheme 13 [33] illustrate some important features of the mechanisms that operate. Firstly there is the question of the mechanism of the replacement of the substituent. This is in part dictated by the type of nucleophile used. If the nucleophile is very reactive i.e. a carbon nucleophile derived from acids of $pK_a > 22$, deprotonation may occur; in addition hydrogen shifts are possible. If the addition of the nucleophile is reversible then there is no control over the regioselectivity of the reaction [scheme 14]. Furthermore, protonation of compound (8), gives rise to the metastable cyclohexadienyl chromiumtricarbonyl species in which hydride shifts allow the production of *ortho*, *meta* or *para* substituted products.

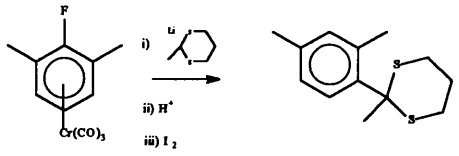


Scheme 14

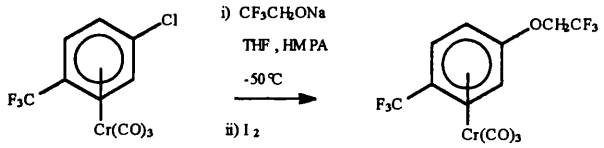
If the conditions selected are suitable, some very impressive S_NAr reactions can be accomplished [scheme 15] [35]. On the other hand straight forward *ipso* substitution can also be achieved with great selectivity [scheme 16] [36]. Together the two alternatives provide a very effective synthetic tool.

It is important to note here the definition of the three terms *ipso*, *cine* and *tele* for S_NAr used here. The IUPAC definition of *ipso* is defined as the replacement of the leaving group by the nucleophile at the atom (carbon) that originally bears the leaving group i.e. direct replacement [Scheme 13 shows two examples where the majority of the replacements are *ipso*]. *Cine* and *tele* are where the nucleophile ends up attached to atoms (carbons) that were not the bearer of the leaving group. For *cine* substitution to occur the nucleophile is positioned only one atom (carbon) away from the leaving group bearer and for *tele* the nucleophile is positioned two or more atoms (carbons) away. Thus

scheme 13 gives *cine* substitution as minor products and scheme 14 gives exclusively *tele* substitution products.



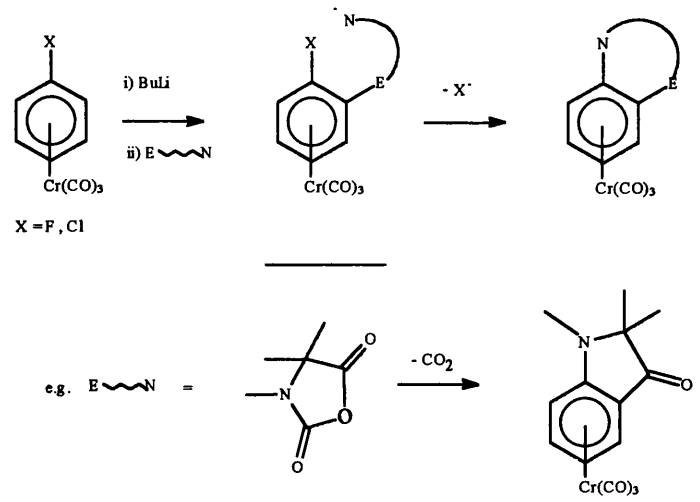
Scheme 15



Scheme 16

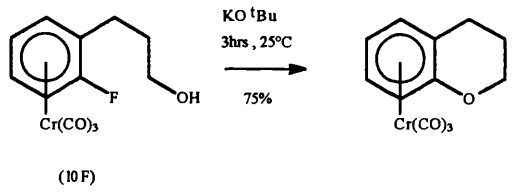
Indeed, successive reactions can be induced, as in an intermolecular palladium mediated halogen replacement sequence which leads to thermally stable polymers [37].

Of course intramolecular halogen replacements give rise to cyclic products. Often generation of the intermediates makes use of the acidity of the arene protons, coupled with a tendency for *ortho* metallation. A general annulation reaction is outlined in scheme 17. Here the metallation and regioselectivity of the reaction are increased in the chromium complex compared to the free arene [38]. The replacement of halide ion by oxygen nucleophiles has been shown to be strongly favoured by the addition of phase transfer catalysts [38].



Scheme 17

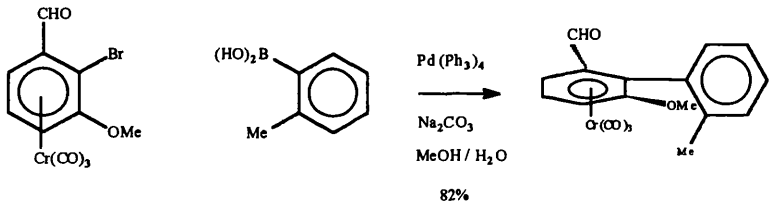
Further examples of inter and intramolecular reactions are encountered in the generation of crown ethers [39], where three intermolecular reactions are followed by an intramolecular. Another illustration is to be found in cyclisation of the hydroxy fluoro compound (10F) by treatment with potassium t-butoxide in DMSO [scheme 18] [40]. The potentially useful replacement of halogens by hydride ion has sadly not been achieved successfully. Similarly, halide exchange also fails [50].



Scheme 18

(1.4.1.1) ***CROSS-COUPLING REACTIONS***

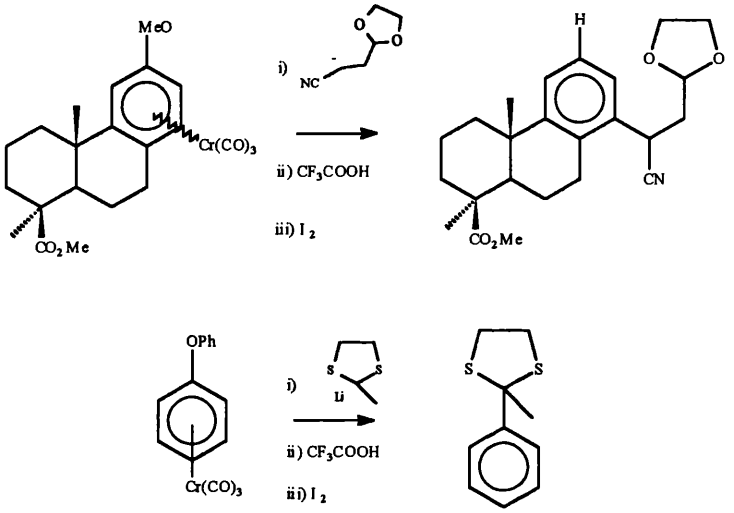
Cross coupling reactions of tricarbonyl(η^6-halobenzene)chromium complexes with aryl metals in the presence of palladium (0) catalysts produced mono-$Cr(CO)_3$ complexes of biphenyl compounds in reportedly good yields [4]. *Ortho*-substituted phenylboric acid derivatives with (2,6-substituted-1-halobenzene) complexes gave stereoselective reactions producing only one of the two possible atropisomers (the definition of atropisomers is when the two rings of a biphenyl are connected by a bridge and rotation about this bridge is impossible or greatly slowed. Naturally the substitution of the rings need to be non symmetrical for the molecule to exhibit chirality [see J.March., *Advanced Organic Chemistry, Third Edition*, John Wiley & Sons). The choice of isomer formed is due, presumably, to the steric interactions between the metal unit and the boric acid. Scheme 19 shows the outcome for one such reaction.



Scheme 19

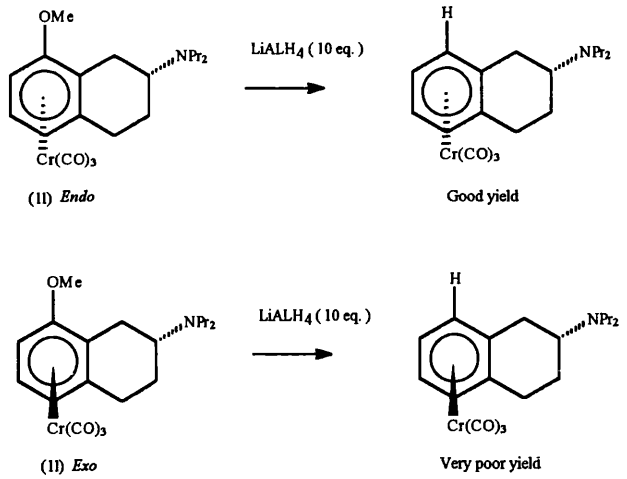
(1.4.2) *S_NAr REPLACEMENT OF OXYGEN*

The replacement of alkoxide ion with nucleophilic carbon anions stabilised by cyanide or dithianyl may under appropriate conditions lead to *ipso*, *cine* or *tele* substitution [scheme 20][42]. Note that the replacement of the o-bonded *p*-toluenesulphonyl group does not take place under these conditions. This is probably due to adverse steric interactions in the intermediate cyclohexadienyl adduct [43].



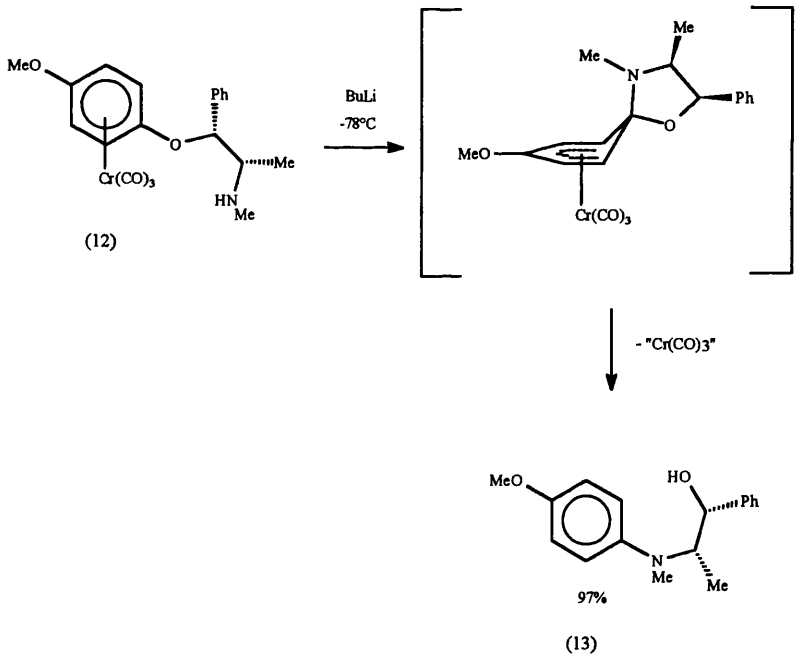
Scheme 20

Replacement of alkoxide has an added advantage over the replacement of halogen in that hydride can now be used as a nucleophile. Super hydride (in the form of $LiBEt_3H$) has been shown to replace methoxide from the electron rich 1,3,5-trimethoxybenzenechromium tricarbonyl complex to give benzenechromium tricarbonyl [44]. Indeed hydride is also known to add to the benzene complex itself. Proof of this is the isolation of the η^5-cyclohexadienyl anion [45]. The synergistic effect of a proximal Lewis base in promoting alkoxide replacement, presumably due to chelation to aluminium has been demonstrated since the *endo* complex of (11) reacts faster than that of the corresponding *exo* complex [46][scheme 21].



Scheme 21

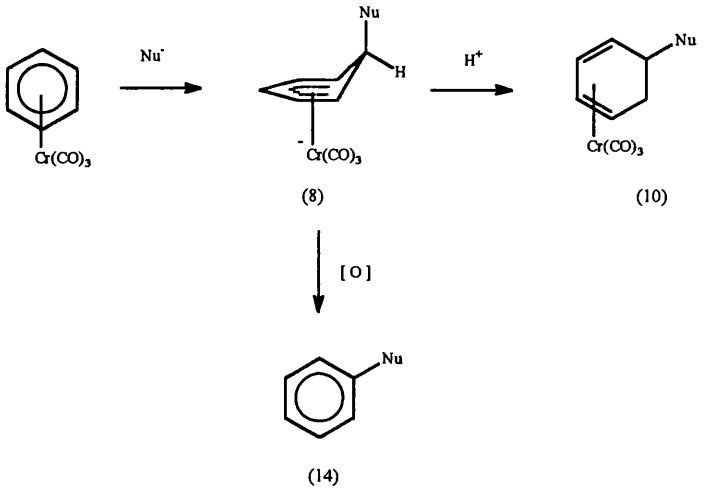
A recent example of ether linkage replacement by Davies [92] proceeds by *ipso* attack (entropic preference) and leads on to an alkoxide *versus* amide anion intermediate. Here the intermediate *p*-methoxy derivative (12) undergoes a Smiles type rearrangement to give the β-aminoalkyl aryl ether (13) in near quantitative yield [scheme 22].



Scheme 22

(1.4.3) *S_NAr REPLACEMENT OF HYDROGEN (ADDITION \ OXIDATION)*

Anions derived from carbon acids with a pka >> 22 [48] are sufficiently reactive nucleophiles to add directly to even unfunctionalised arenechromium complexes. This leads to the production of cyclohexadienyl anionic complexes (8) that can be protonated, giving cyclohexadiene complexes (10), or through oxidation to the arene product (14) [scheme 23].



Scheme 23

In the last process this is formally a S_NAr reaction with hydride ion being the leaving group. The success of this reaction depends upon the nucleophile used, and many organolithium reagents effect simple deprotonation (effectively metallation: as noted and used earlier [scheme 17]) . Grignard reagents add to a CO ligand on the metal. Although carbon anions from sulfoxides are inert [49], others are clearly reactive and the remaining discussion will focus on their chemistry.

Due to the reactivity of the nucleophiles, equilibriation between the cyclohexadienyl anion and the starting complex is a concern and it is also unclear if thermodynamic or kinetic control is the operating factor for the addition of many nucleophiles [47]. However, in practice regioselectivity can normally be predicted from an assessment of solvent, temperature and the electronic and steric properties of the nucleophile and complex.

Some examples serve to clarify this statement: Mono substituted arenes with groups capable of electron donation such as amino, methoxy or fluoro (which is only a resonance donor), show strong preference for *meta* addition. This may be seen as the entry of the nucleophile at the least electron rich site as predicted on the grounds of the resonance effect of the substituents. This is in contrast to M.O. calculations which indicate increased LUMO density at the *ortho* and *meta* positions [50] with *ortho* being the largest i.e. a preference for *ortho* attack.

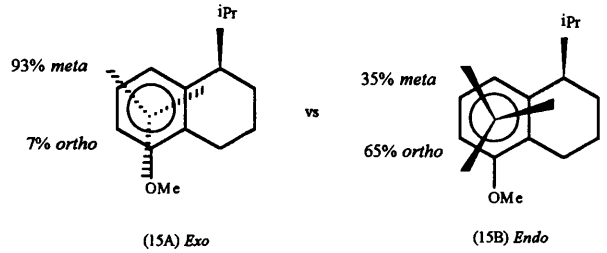
Indeed alkyl and chloro groups [51] do have the effect of promoting both *ortho* and *meta* substitution and here addition may be less favoured when the nucleophile is large [table 1].

Anion	Mono Substituent of complex	Ratio (o:m:p)
$LiCH_2CN$	Me	35:63:2
$LiC(Me)_2CN$	Me	1:97:2
$LiCH_2CO_2{}^tBu$	Me	28:72:0
$LiCH_2CO_2{}^tBu$	Cl	54:45:1
$LiC(Me)_2CO_2{}^tBu$	Cl	53:46:1
$LiCH_2CO{}^tBu$	Cl	70:24:6
LiC(CN)Me)(OC(Me)OEt)	CF_3	0:30:70
$LiC(Me)_2CN$	$SiMe_3$	0:2:98

Table (1)

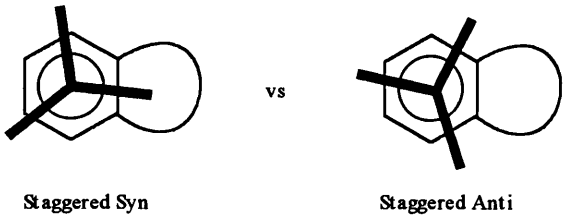
Para directing substituents are rare as electron withdrawing groups (e.g. acyl and cyano) tend to direct reaction to the substituent itself rather than at the nucleus. Successful *para* directing groups are CF_3 and TMS.

In disubstituted arenes the regioselectivity is more difficult to analyse, but often only one isomer is formed. Here the effect of the η^6-bonded chromium tricarbonyl is predominant; thus, the tripod can adopt either a staggered or an eclipsed conformation depending on the substrates. For example, two isomers of 1-methoxy-5,6,7,8-tetrahydro-5β-isopropylnaphthalene are known: the *exo*-form (15A) and the *endo*-form (15B). Irreversible nucleophilic attack by lithio-1,3-dithiane at -78°C on the *exo* form occurs mainly *meta* to the methoxy group, but with the *endo* form the *ortho* adduct is favoured [scheme 24]. It is considered that the preferred conformation of the carbon monoxide tripod with respect to the nucleus of the *exo*-form is eclipsed and this enhances the electrophilicity of the carbon atoms overlapped by the CO ligands. It is this increased affinity for a nucleophile that directs attack to the C-3 site [148].



Scheme 24

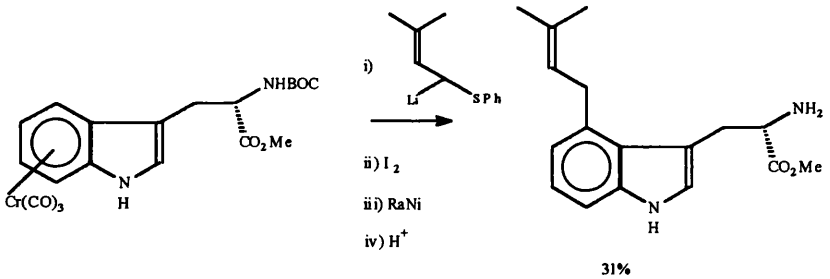
In line with this the conformational preferences, staggered *versus* eclipsed, are overwhelmed by higher and longer reaction times and *meta* attack occurs for both *exo* and *endo* forms. It should be noted that for symmetrically disubstituted arenes the complexes adopt either the syn or the anti staggered conformers [scheme 25] favouring neither position [53].



Scheme 25

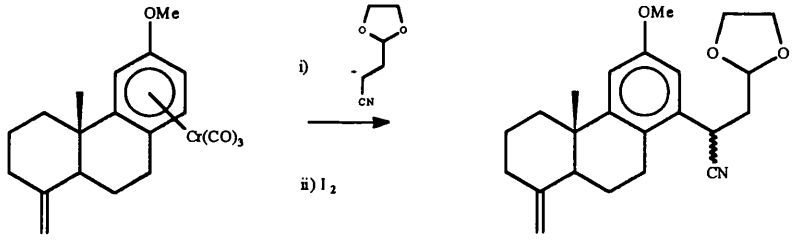
Solvent effects are pronounced: for example the reaction of [N-methyl(tetrahydroquinoline)$Cr(CO)_3$] and 2-lithio-2-cyanopropane at -78°C gives a C-5:C-3 product ratio of > 96:1. If sufficient time for equilibriation is allowed this reaction changes to ca 2:1, but the addition of HMPA reduces the initial preference to 54:44 and retards the equilibration. Presumably HMPA interacts with the reaction intermediates and has the effect of equalising their energy contents. Other examples of this type of behaviour has been documented [52, 54, 55], and further discussion of the conformational behaviour of the η^6-arene complexes can be found in references 56, 57 and 58.

Enough has been said to indicate the role that nucleophilic substitution of arene chromium complexes might play in synthesis and it remains to exemplify that this is the case [see scheme 26 for more examples].



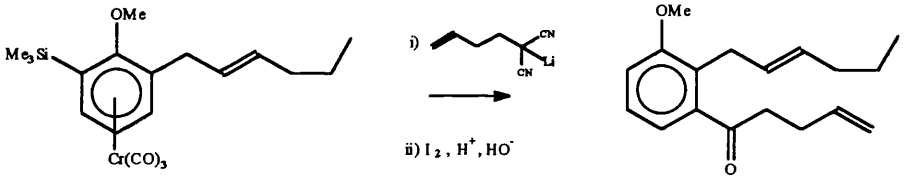
31%

Regio and Chemoselectivity ''



92%

Regioselective ''



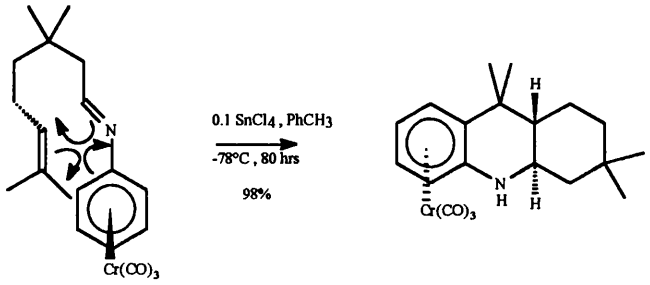
61%

Regioselective ''

Scheme 26

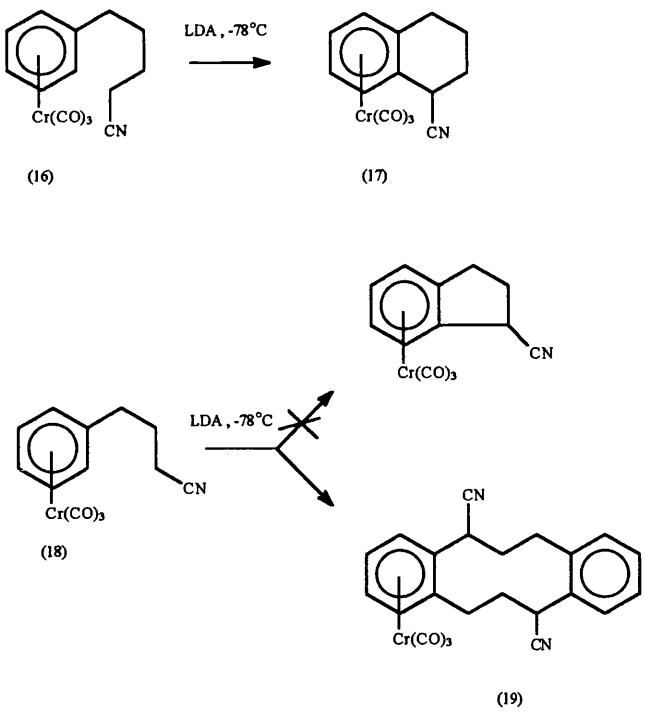
(1.4.3.1) *S_NAr INTRAMOLECULAR HYDROGEN REPLACEMENT*

There are only a few examples of intramolecular cyclisations, but they are significant illustrations of the power of the approach. The first is part of a Lewis acid catalyzed hetro-Diels-Alder reaction with an (imino-η^6-arene)$Cr(CO)_3$ complex where a non-activated alkenyl side chain acts as the diene component. Since the dienophile can only approach the diene from the opposite face to the tricarbonylchromium group a diastereoselective intramolecular cycloaddition resulted giving a *trans* ring junction [scheme 27] [59].



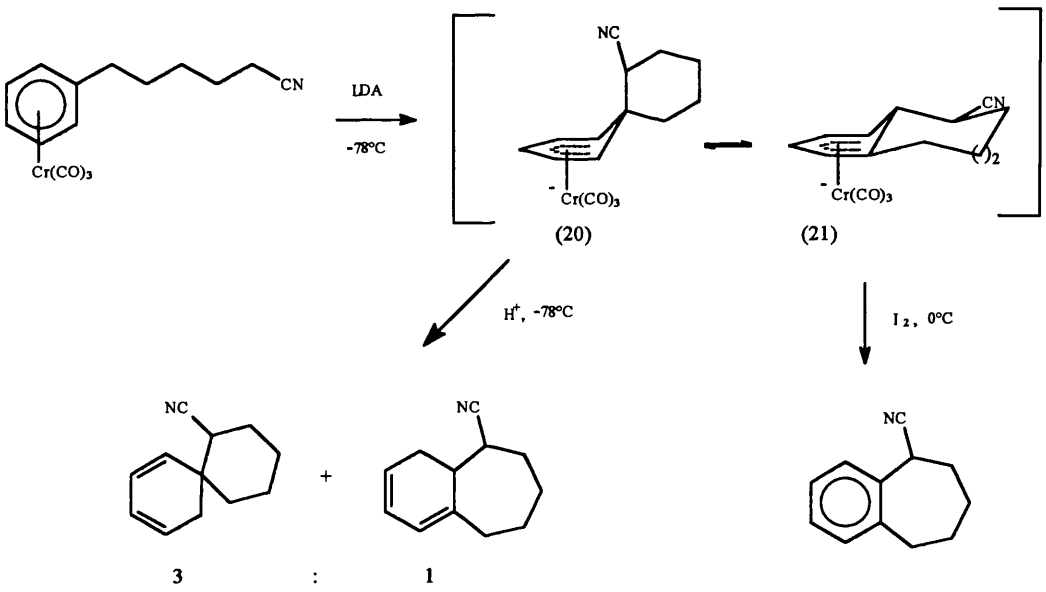
Scheme 27

The second example [scheme 28] is more simple and is a development of related intermolecular procedures. Here the anion from the complex (16) cyclises to give (17) in 86% yield. The conditions are exceptionally mild, but the reaction fails when the side chain is reduced to three methylene units. Now the starting complex (18) on deprotonation yields only the intermolecular product (19). It seems therefore that the extra strain in a 6,5 fused product exceeds the energy available for intramolecular attack and an alternate reaction path is adopted.



Scheme 28

Extension of the carbon chain to five methylenes complicates the picture even more giving rise to a mixture of the spirocyclic and fused ring isomers (20) and (21) [scheme 29] [50].



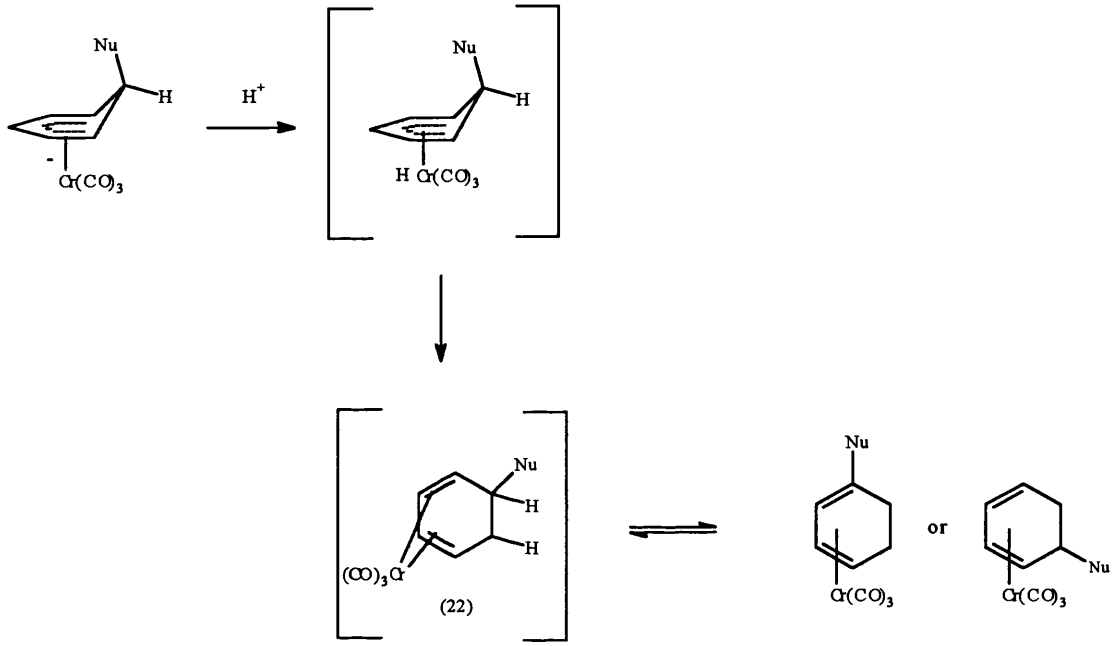
Scheme 29

(1.5) *S_NAr DOUBLE ADDITION/ DE-AROMATISATION*

Tandem nucleophilic addition and electrophilic quenching of the product anion has often been used; such procedures also effect re-aromatisation. Below is a survey of the types of electrophiles that have been used in such reactions but first the factors that give rise to this type of di-functionalization need analysing. The addition of a nucleophile, to generate a cyclohexadienyl complex (8) needs to be almost irreversible so that electrophilic quenching does not end in a nucleophile-electrophile reaction. Irreversibility necessarily needs the use of carbon acids of $pk_a > 22$ and good solvation of the nucleophile cations i.e. use of solvents such as THF and for further control of equilibriation, HMPA or DMPU.

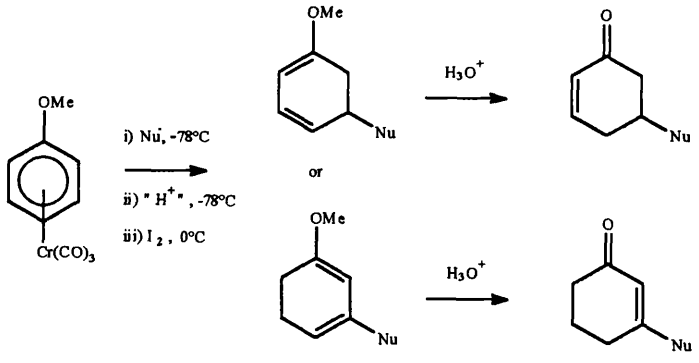
(1.5.1) *PROTONS AS ELECTROPHILES*

With a proton source to quench the intermediate cyclohexadienyl anion (most commonly TFA [61]) the product is a cyclohexadienyl complex (22) which is susceptible to rearrangement leading to 1 or 5 substituted 1,3 cyclohexadienes. Here the isomer distribution depends only upon their relative stabilities. Overall this process is complementary to the Birch reduction/alkylation reaction [scheme 30].



Scheme 30

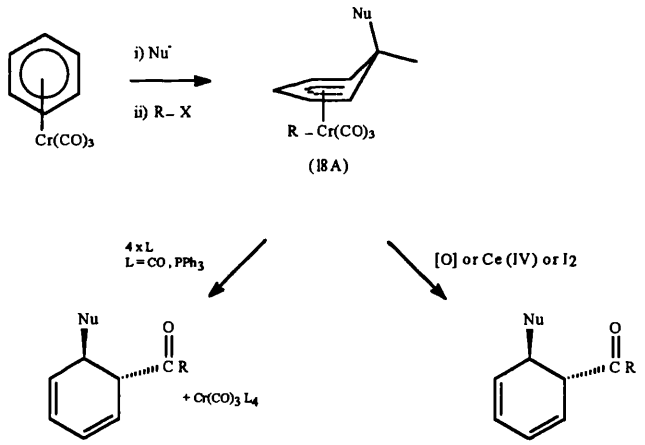
The overall reduction process can be reversed by oxidation with DDQ [48] to effect a S_NAr reaction with hydride ion as the leaving group. Although the double addition/de-aromatisation could well be a general reaction, it has so far been restricted to anisole derivatives and hence, through hydration, to the synthesis of 5-substituted cyclohex-2-en-1-ones [61 - 64]. The position of the double bond in the products can be controlled selectively depending on the conditions of the acid treatment and the acid hydrolysis [scheme 31].


OMe
Cr(CO)3
i) Nu, -78°C
ii) " H+ ", -78°C
iii) I2 , 0°C
OMe
Nu
or
OMe
Nu
H3O+
H3O+
O
Nu
O
Nu

Scheme 31

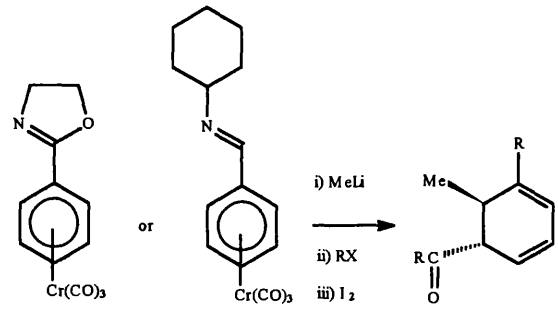
(1.5.2) *CARBON AS THE ELECTROPHILE (ACYL MIGRATION)*

In contrast to protonation, quenching of cyclohexadienyl anions with carbon electrophiles occurs at the metal atom. This is followed by insertion into a CO ligand and acyl rearrangement into the ring. The final product is a *trans*-1,2-cyclohexadiene since the acyl group is delivered intramolecularly [scheme 32]. Efficient nucleophiles are primary iodides, primary triflates, allyl bromide and benzyl bromide. The acyl migration step can be induced by the "addition" of extra ligands [65]. Although triphenylphosphine is effective, the use of carbon monoxide at a moderate pressure (ca. 4 bar) is the preferred method since such reactions are cleaner, the yields are higher and the $Cr(CO)_6$ can be recovered [66, 67]. An alternative route is the direct oxidation of the addition product (18A) with iodine or cerium (IV) [scheme 32].



Scheme 32

It must be noted that simple alkyl lithium reagents (MeLi, BuLi, PhLi, ^{t}BuLi, CH_2=CHLi, $LiCH_2COO^tBu$), which normally deprotonate chromium complexes add with high *ortho* regioselectivity to an oxazoline or an imine substituent [67]. Combined with electrophilic quenching and subsequent acyl migration such a reaction gives 1,5,6-trisubstituted cyclohexadienes with excellent stereo and regiocontrol [68] [scheme 33].



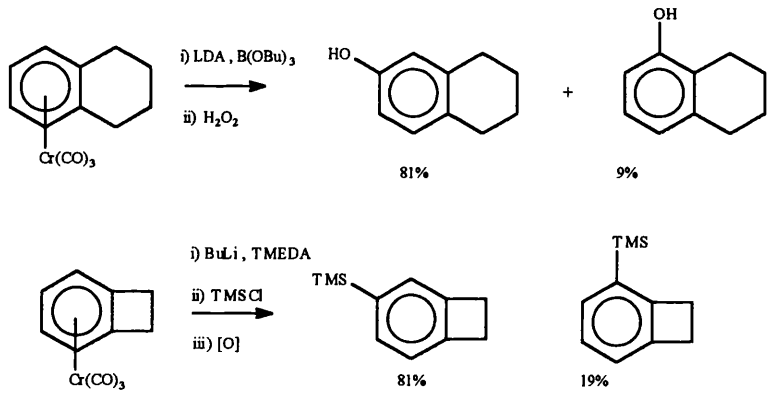
Scheme 33

(1.6) *THE GENERATION AND THE USE OF 'METAL STABILISED' IONS*

It is well known that the generation of benzylic anions and cations from chromium complexed substrates is relatively easy and the ions produced are stabilised by the charge delocalisation with the nucleus or the metal.

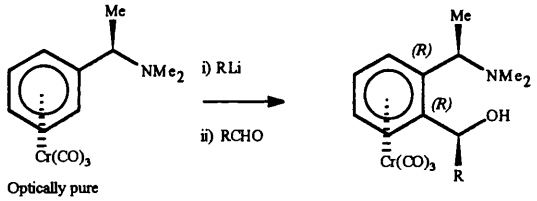
(1.6.1) *ARENE DEPROTONATION*

Removal of a proton from the nucleus of a chromium complex can be carried out with strong base, such as alkyl lithium reagents in the presence of a good solvent for the chelation of the lithium counter ion (i.e. THF, HMPA, TMEDA). Deprotonation and subsequent electrophilic quenching does not affect the aromaticity of the arene and is thus complementary to the nucleophilic addition/oxidation technique mentioned earlier (replacement of hydrogen). Of course as electrophiles are the source of the new bonds, different functionalisation can be achieved. Procedures in which the base and an electrophile are simultaneously present are the basis of the regioselective hydroxylation, silylation, or ethoxycarbonylation of the complexes of some polycyclic arenes. Regioselectivity is dependant upon both the electrophile and the substrate [69, 70][scheme 34].



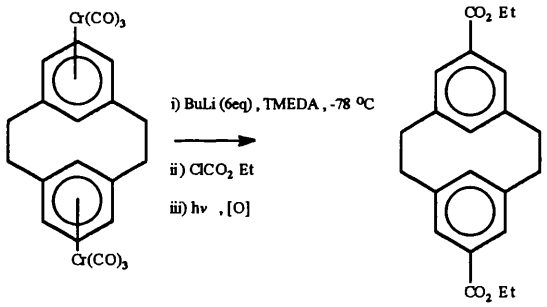
Scheme 34

If the substrate contains an oxygen, nitrogen or a halogen atom at the benzylic site *ortho*-lithiation and reaction with an eletrophile normally gives *ortho* substitution products. This is directly comparable to *ortho* lithiation techniques used on non-complexed substrates, although here the yields are generally higher and side reactions are minimised. *Ortho* lithiation of an optically active complex subtending a benzylic tertiary amine and then reaction with an aldehyde gives products with excellent diastereoselectivity [71][scheme 35].



Scheme 35

A more complex and interesting example is found in the "one-pot" difunctionalisation of the (2,2) metacyclophane *bis*-chromiun complex [scheme 36]. Here the deprotonation gives a dianion which may be quenched regiospecifically with ethyl chloroformate to afford the corresponding diester [72].

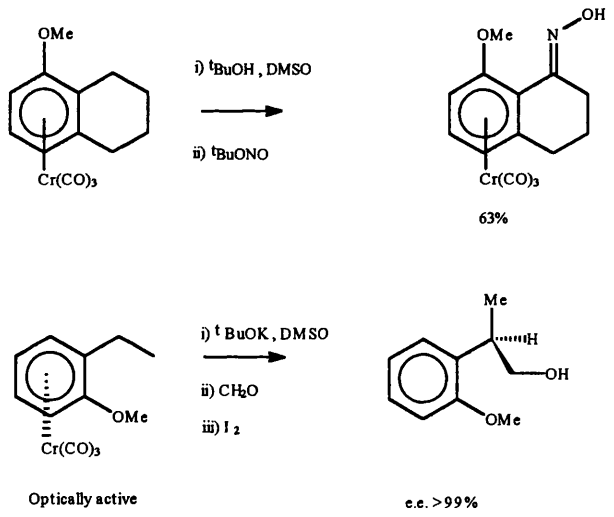


Scheme 36

(1.6.2) ***BENZYLIC DEPROTONATION.***

Toluene complexes can be deprotonated by treatment with bases such as BuLi, LDA or ^{t}BuOK. Subsequent quenching can be effected with a range of electrophiles and with enones, both 1,2- and 1,4- additions are noted [73]. The last being promoted if copper (I) is present. Nitrosation leads to the synthesis of oximes [74]; thus the complex of 8-methoxytetralin reacts at C-1 as a consequence of the electron donating methoxy substituent de-stabilising the alternative C-4 benzylic anion [scheme 37].

Benzylic hydroxymethylation of chiral substrates occurs with high or even complete enantioselectivity, for example (R)-2-(2-methoxyphenyl)propan-1-ol can be synthesised from the appropriate enantiomer of ethylbenzene chromium tricarbonyl, by deprotonation and reaction with formaldehyde [75].

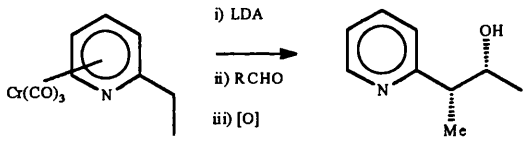


Scheme 37

Consecutive deprotonation/alkylation steps have been shown to occur both regio and stereoselectivly to generate important natural products [76,77] and have a great scope in potential synthesis. Anions have also been generated via deprotonation of some (η^6-allylbenzene)Cr(CO)$_3$ complexes using ^{t}BuOK/THF or NaH/DMF or phase transfer catalysis [78]. These can be quenched with carbonyl compounds at either the alpha or the gamma site depending upon the reactants. These results differ

from those obtained for the reactions of the anions of non-complexed allylbenzenes with carbonyl compounds, where attack is normally predominant at the benzylic carbon atom. This may well reflect the steric bulk of the tripod.

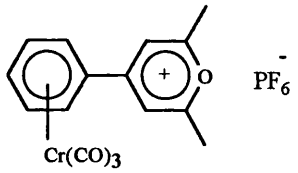
There are even cases of hetero-aromatic compounds undergoing this sequence of benzylic deprotonation followed by electrophilic quenching with non-enolizable aldehydes. In the case of the 2-ethylpyridine complex the relative stereochemistry of the products is predictable from a consideration of Cram's rule [79] [scheme 38].



Scheme 38

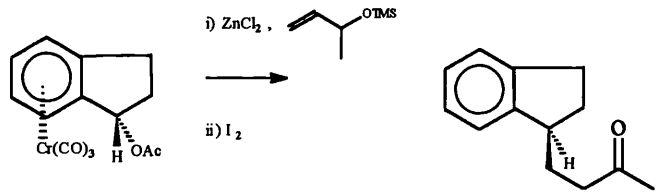
(1.6.3) *BENZYLIC CATIONS*

Again the stability of this ion is increased by the presence of the chromium tricarbonyl group. Both NMR data and computational evidence indicate that the 4-(η^6 -C_6H_5)$Cr(CO)_3$ unit of the γ-Benchrotrene pyrylium salt is electron donating towards the benzylic cation [see below for structure][80].



The γ benchrotrene pyrilium ion

Again the approach of the nucleophile is controlled by the steric bulk of the $Cr(CO)_3$ tripod. This selectivity is exemplified by the following example, where the *endo* acetoxy group is displaced from the benzylic site to generate a cation which is then quenched quantitatively from the *exo* face. When the substrate is optically pure then the product is also chiral and the reaction has been described as "the enantioselective alpha-alkylation of a carbonyl compound by an optically active carbocation possessing planar chirality" [81][scheme 39].

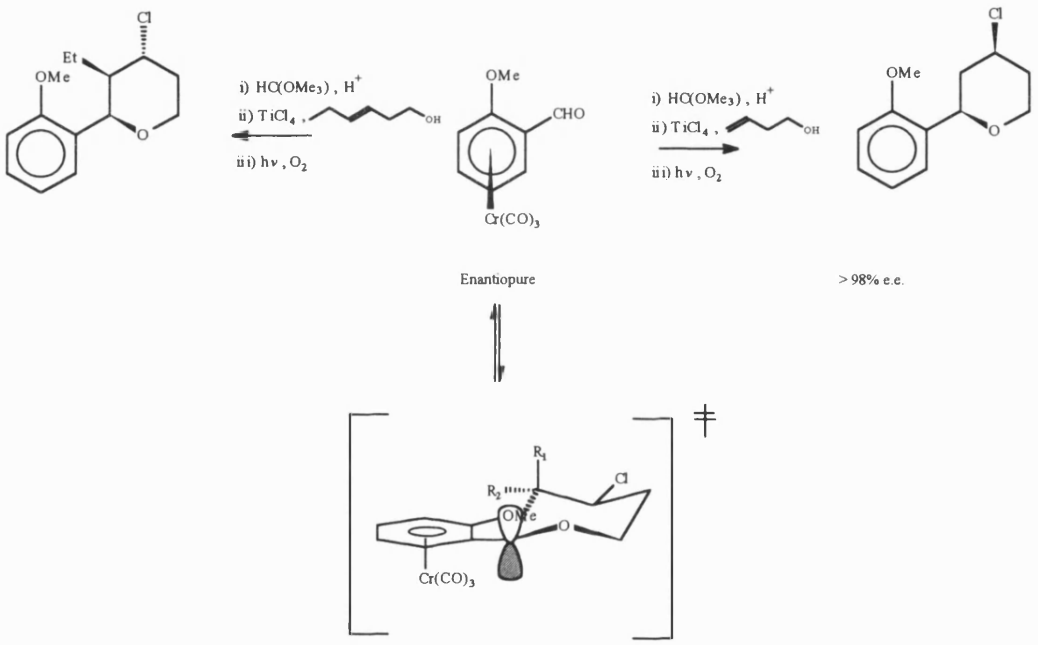


Enantiopure

Scheme 39

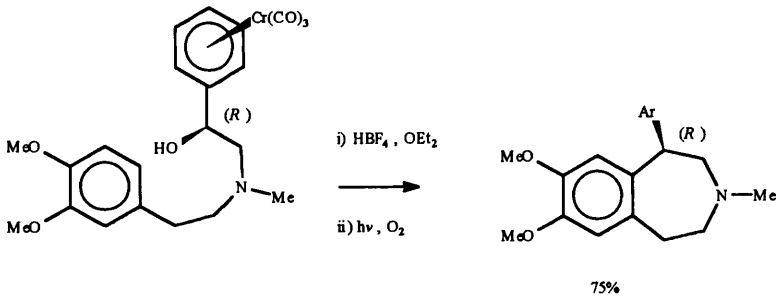
Other examples of this type are known; thus, enantiomers of the chromium complex of 2-methoxybenzaldehyde can be acylated and in the presence of a Lewis acid reacted with 3-butenol to give enantiomers of 4-chloro-2-(2-methoxyphenyl)tetrahydropyran.

The transition state for this reaction adopts a chair conformation, such that the large aryl unit adopts a pseudo equatorial site. Cyclisation proceeds through attack of chloride at C-4 in a *trans*-antiperiplanar mode. Thus two chiral centres are controlled at once and this can be extended to three should the alkenol contain a branched chain [scheme 40][123].



Scheme 40

Scheme 41 shows another hetrocyclisation, the stereochemistry of which is determined by the orientation of the metal ligand, in the absence of the metal the mirror image of the benzoazepine is produced [82].



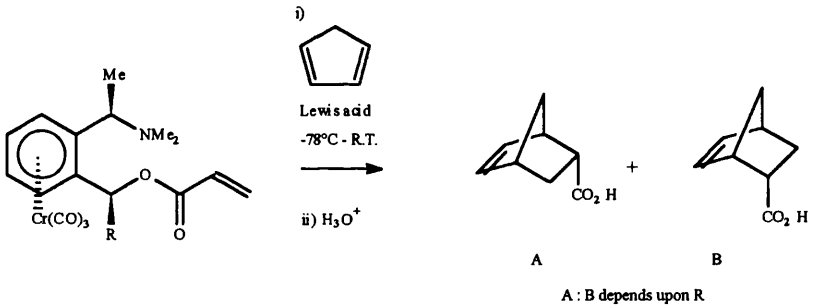
Scheme 41

(1.7.1) *REACTIONS EXTERNAL TO THE ARENE π SYSTEM*

So far the examples presented have been mainly concerned with reactions directly involving the π-system to which the $Cr(CO)_3$ unit is bonded. However the effect of complexation can influence chemical reactivity at more remote centres.

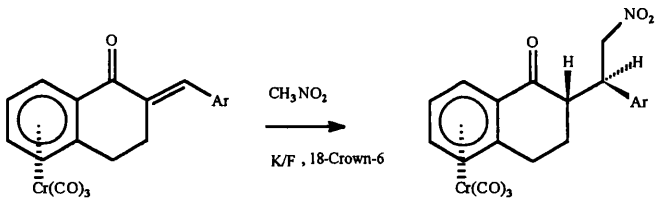
The first and possibly the most obvious effect of the $Cr(CO)_3$ unit is its steric bulk.

There are several examples where the stereochemical outcome of a particular reaction is determined by the spatial demands of the metal tripod [59, 84 - 90]. Cyclisation of a tethered imine has been noted earlier [59], but another good example in which the facial selectivity (often *endo:exo*> 99:1) is strongly influenced by the steric bulk of the dienophile is in the illustration shown in scheme 42 [86] where the dienophile is chiral and acts as an auxiliary to induce asymmetry into the product.



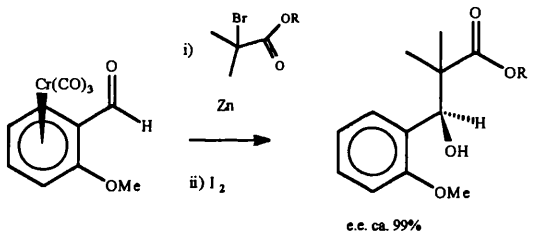
Scheme 42

Conjugate addition to an enone, also mediated by a metallated arene unit bonded to the carbonyl group [Scheme 43] shows just such a process where diastereoselectivity is controlled at a centre four bonds from the η^6-complexed arene [85, 86].



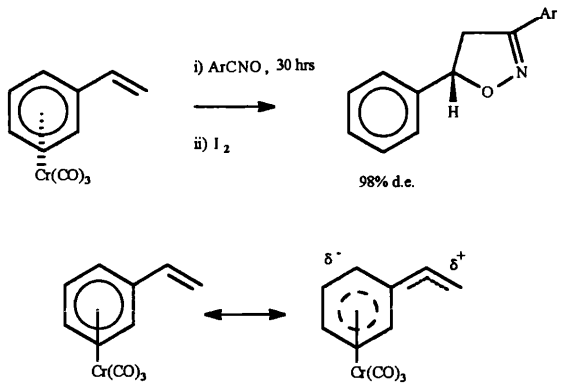
Scheme 43

Much less dramatic are the many examples where the addition of a nucleophile to an arylaldehyde is known to produce diastereoselectively enriched products. Again this is directly due to the steric effects of the tripod, but these reactions are only useful when there is an *ortho* substituent [scheme 44] [89].



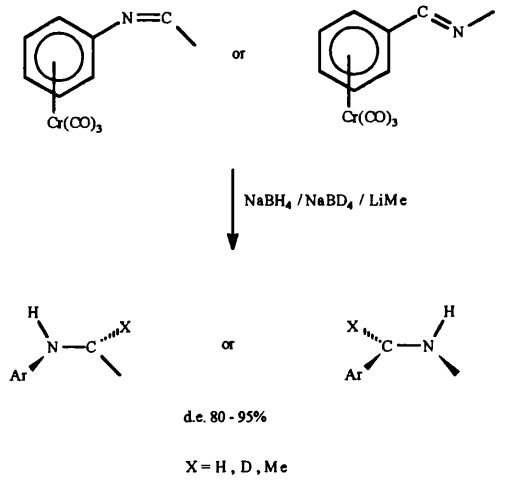
Scheme 44

Complexed styrenes show anti-Markownikov chemoselectivity appropriate to that of the parent compound. A good example of this type of behaviour is the addition of the cyano stabilised carbon nucleophile shown in scheme 47 (the intermediate carries the negative charge at the benzylic position which is contrary to Markownikov addition). In the addition the electron affinity of the metal decreases the electron density of the double bond so that nucleophiles can attack at the β-position. The intermediate anion is then resonance stabilised, and can be quenched by electrophiles. An illustration is shown in scheme 45 where the complex of styrene itself is reacted with arylnitrile oxides to give, after decomplexation the corresponding isoxazolines. (NB. this is a 1,3 dipolar addition and as such the regiochemistry is defined by the addition of the negative end of the dipolarphile at the β position of the styrene [90]).



Scheme 45

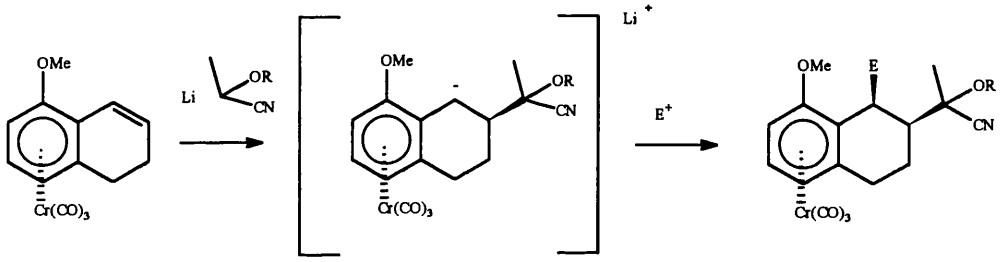
A more recent example is presented in scheme 46 where the reduction of arylimines (azastyrenes) occurs with high diastereoselectivity, an effect due to nucleophilic attack occurring on the face of the imine anti to the metal [146].



Scheme 46

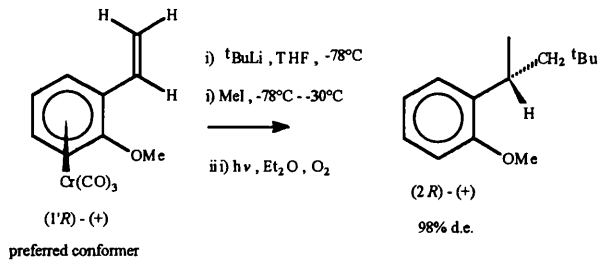
(1.7.2) *ADDITION-ELECTROPHILIC TRAPPING OF STYRENES*

As noted, polarisation of the styrene double bond by the metal tripod and it's ability to stabilise benzyl anions leads to the selective addition of anions at the β position. Carbanions (often alkyl lithiums) are suitable and the intermediates can be protonated or trapped alpha giving *cis* 1,2-disubstituted products. So far only methyl iodide, acetyl chloride and diphenyl disulphide have been used in place of acids, but there is no reason to think that others would not be satisfactory [91]. When appropriate the relative stereochemistry of the addition is always anti to the metal tripod[1, 83, 91, 92]. This is the case for a dihydronaphthalene as illustrated in scheme 47 [91]. In this reaction it was noted that the initial attack of the anion was reversible.



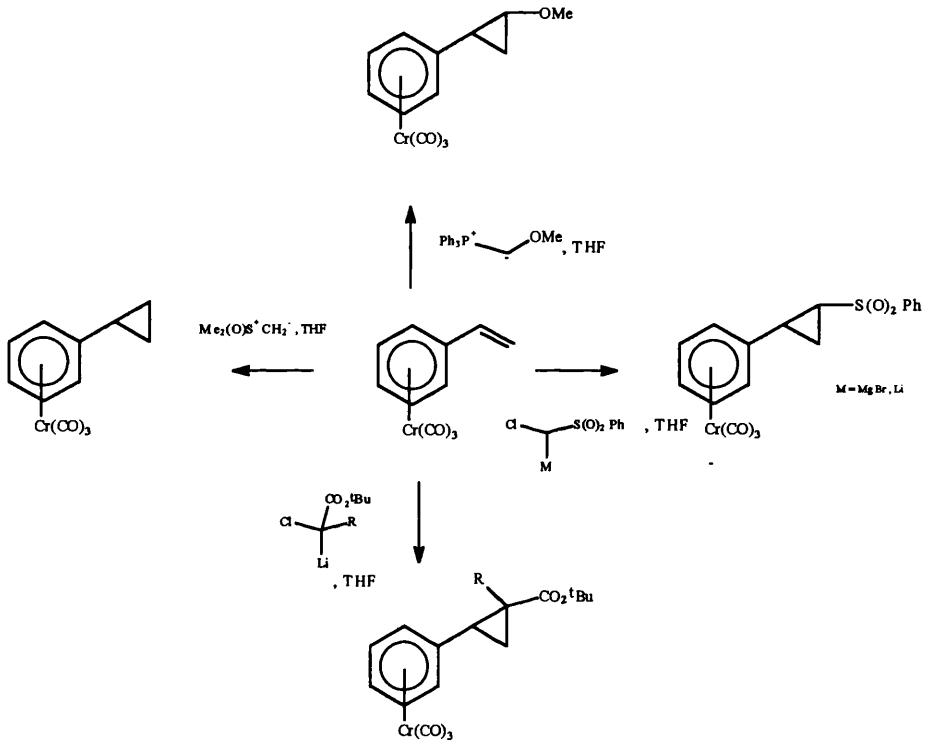
Scheme 47

Two recent papers further exemplify the approach: Davies et al.[92] have shown that homochiral (1'R)-(+)-(2-methoxystyrene)chromiumtricarbonyl undergoes a completely stereoselective tandem nucleophilic/electrophilic addition sequence with ^{t}BuLi and methyl iodide as reagents. This generates after decomplexation, (2R)-(+)-2-(2-methoxyphenyl)-4,4-dimethylpentane (e.e > 99%) [scheme 48].



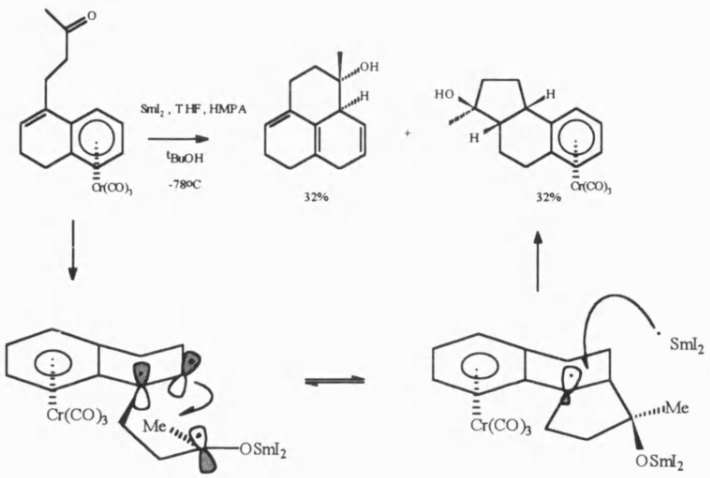
Scheme 48

Gibson et al.[147] have devised a novel route to cyclopropanation that involves the intramolecular cyclisation of the intermediate carbanion, formed after addition of the nucleophile. This requires the presence of a leaving group in the reagent and it has been shown that sulfur and phosphorus ylides and α-chloro carbanions are quite useful [scheme 49].



Scheme 49

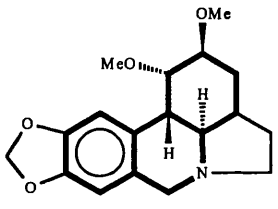
Finally, there has been a recent report of a radical induced reaction which in addition to a styrene derivative also affords a benzoperhydroindane. Both products are obtained by alternative ring closures of the radical formed by single electron transfer from samarium diiodide to the carbonyl group of the chromiumtricarbonyl complex of 1-(2-oxobutyl)-3,4-dihydronaphthalene. The benzoindane is unexpected since its formation depends on an unfavourable 5-*endo*-trig cyclisation. Nevertheless the relative stereochemistry is analysed on the basis that the solvated samarium unit resides anti to the metal tripod, whereas the methyl group is orientated syn [94] [scheme 50].


O
SmI2 , THF, HMPA
tBuOH
-78°C
Cr(CO)3
OH
H
32%
HO
H
H
32%
Cr(CO)3
Cr(CO)3
Me
OSmI2
SmI2
Cr(CO)3
Me
OSmI2

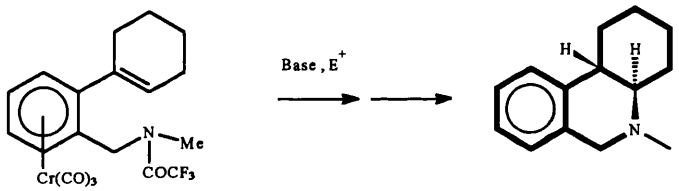
Scheme 50

(2.1) 6-*Endo*-trig cyclisation

Scheme 51 shows the expected 6-*endo*-trig cyclisation of compound (23) that was proposed as the first step in this study. It can be seen that the external double bond of the styrene unit is now independently enclosed in the cyclohexane ring and the heteroatom for the cyclisation is of an α–benzylic nature. Enclosing the styrene double bond in another ring means the product would be of the fused 6,6,6 type. This structure is found in a variety of alkaloid natural products such as Lycorime shown below [95]. This leads to the need for the design and synthesis of compound (23).



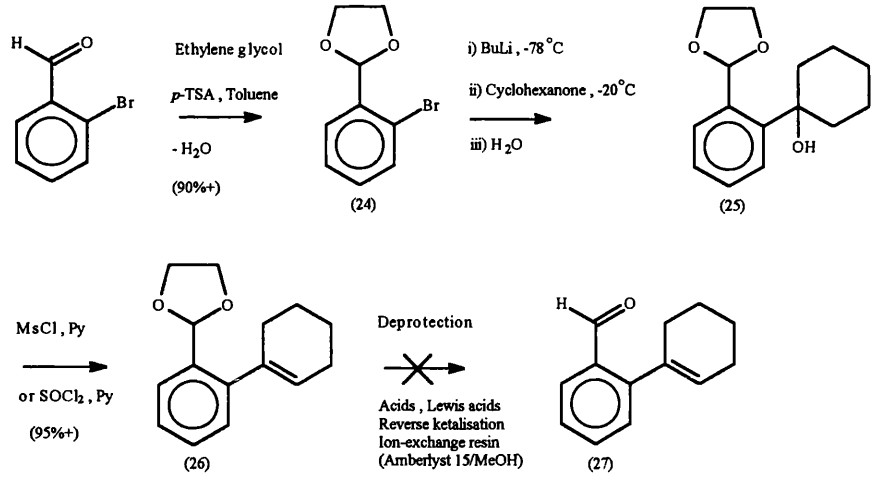
Lycorime



(23)

Scheme 51

The original plan for the synthesis of this compound from 2-bromobenzaldehyde required the lithiation of its acetal (24) and reaction with cyclohexanone. It was expected that dehydration of the resulting alcohol (25) and deprotection of the acetal group would both occur during work up in the presence of acid giving the aldehyde (27) that could be converted into (23) by conventional manipulations [scheme 52].

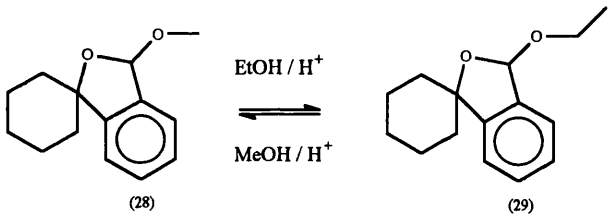


Scheme 52

The first two reactions were carried out successfully, but the envisaged acid catalysed dehydration and deprotection of (25) during the work-up failed to produce the cyclohexenyl aldehyde (27). This was the first indication that problems were to be encountered with this route. Indeed product (25) was apparently stable to a variety of strongly acidic conditions, although treatment with either conc. sulfuric or conc. hydrochloric acids caused the molecule to decompose. This unreactivity towards acids was unexpected at the time but, as later work was to prove, might have been anticipated had we paid more attention to the reaction mechanism. We also attempted to activate the system by converting the alcohol into a good leaving group to assist the production of the alkene acetal (26). This was carried out by treatment of (25) with thionyl chloride/pyridine [96] or with mesyl chloride/pyridine. The first method was the most efficient and gave a high yield (90%+) of (26) as a clean product in a short reaction time.

Once again we experienced considerable difficulties in the deprotection of the acetal group of (26) even though a variety of aqueous, non-aqueous and Lewis acid conditions were tried, including reverse ketalisation and ion-exchange mediated hydrolysis (Amberlyst-15/methanol/H^+). Starting material was returned in each case.

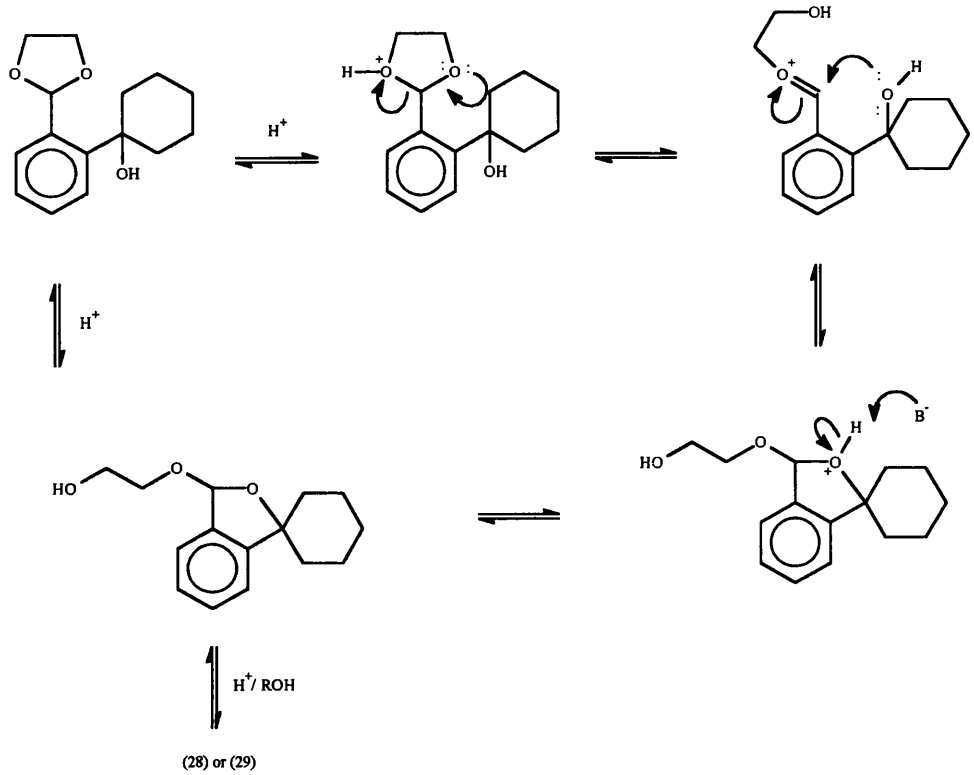
Further attempts were now made to deprotect the acetal alcohol (25) under conditions less likely to promote concomitant dehydration. These included treatment with a variety of aqueous and non aqueous acids in media with Lewis acids. Ion-exchange resins in the presence of either methanol or ethanol in either homogenous or biphasic systems were also employed. None of these methods afforded the alkene (27), but in contact with methanol or ethanol this compound gave the spirocyclic products (28) or (29) [the ethyl group in compound (29) comes from the acid hydrolysis of ethylacetate] which were isolated in near quantitative yields. These products were interconvertable, thus the ethyl compound gave the lower homologue (28) when it was heated in methanol and an acidic ion-exchange resin. Conversely when the methyl analogue was treated with ethanol and an acidic ion-exchange resin the ethyl compound (29) was isolated [Scheme 53].



(28) (29)

Scheme 53

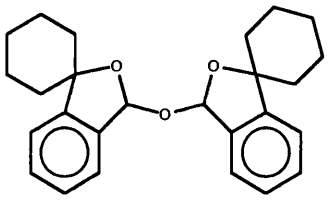
It now seems clear that deacetalation is rapid, but that the oxonium ion or its equivalent, is intercepted by the proximal hydroxyl group before the latter can be protonated and eliminated [scheme 54].



Scheme 54

In the absence of an "external" alcohol it is possible that the intermediate spiro compound could reform the starting tertiary alcohol (25).

Less protic conditions might disfavour this type of reaction, but attempts using Mitsunobu conditions [97], PCl_5, $POCl_3$, Amberlyst-15, sulphuric $acid_{(aq)}$ and $BF_3.OEt_2$ all failed. None of these reactions produced the alkene aldehyde (27), but interestingly when the latter two conditions were tried two identical compounds were produced that were identified as two diastereoisomers of the condensation product (30) [only two as the molecule has C_2 symmetry].



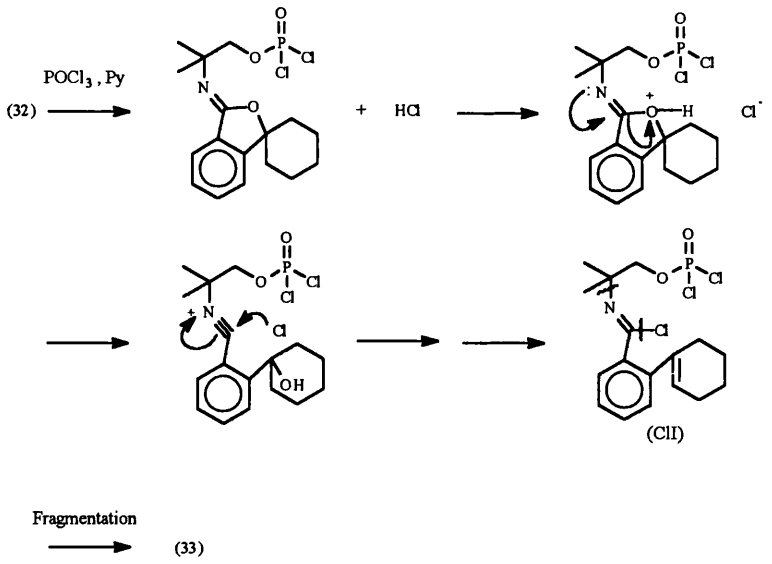
(RR or SS only)

Compound (30)

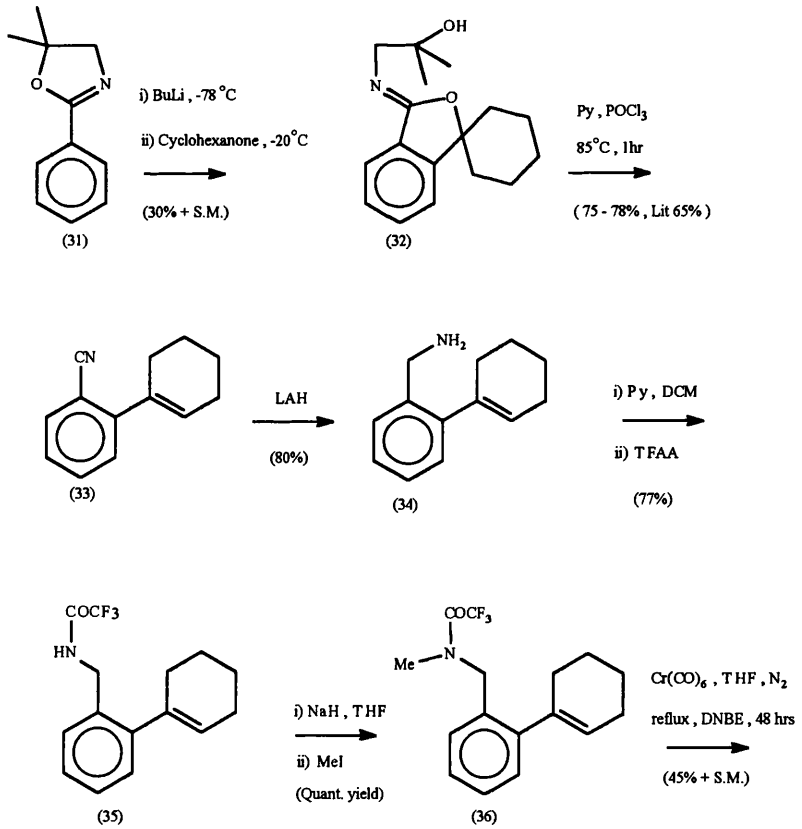
Attempted dehydration of (30) by use of the same reaction conditions as used before to effect the conversion of (28) or (29) to (27) also failed.

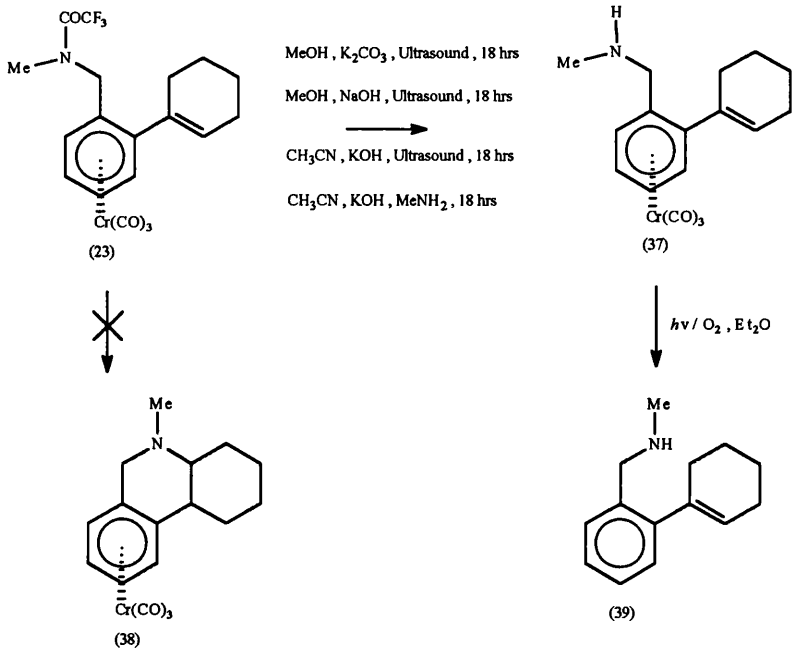
The nitrile (33) is a known compound [98], it has been prepared from the oxazoline (31) by metallation and reaction with cyclohexanone, followed by reaction of the product (32) with phosphorus oxychloride/pyridine. It is interesting to note that (32) is also a spiro compound, showing clearly the propensities of systems of this type to cyclise rather than to dehydrate directly. We now adopted this route since we recognised that reduction [99] of the nitrile would afford the amine (34) and hence our target molecule (36) via the acetamide (35).

The first two steps of the reaction sequence were carried out following literature recommendations [98], but we found the yield of the second reaction was greatly improved and the reaction time reduced if the pyridine/phosphorus oxychloride mixture was heated to reflux. The mechanism of the first step can be easily explained as addition of the lithium alkoxide, generated from the addition of the o-lithiated aromatic to the ketone, entering the electronegative carbon atom that is attached to both the oxygen and the nitrogen. The second step is a little more complicated though. The mechanism [98] has not been studied and a full explanation has not been arrived at although it has been postulated that the phosphorus oxychloride activation of the tertiary alcohol leads to the preparation of the chloro imine intermediate (CII) which undergoes fragmentation under these conditions to liberate the final, dehydrated, nitrile (33). A summary of the postulated mechanism is shown on the next page.



Next, reduction with LAH proceeded smoothly to give the free amine (34) which was N-acetylated with trifluoracetic anhydride (35), N-methylated (36) and finally complexed with chromium hexacarbonyl to produce the target (23) [scheme 55].




COCF3
Me
N
Cr(CO)3
(23)
MeOH , K2CO3 , Ultrasound , 18 hrs
MeOH , NaOH , Ultrasound , 18 hrs
CH3CN , KOH , Ultrasound , 18 hrs
CH3CN , KOH , MeNH2 , 18 hrs
H
Me
N
Cr(CO)3
(37)
hν / O2 , Et2O
Me
N
Cr(CO)3
(38)
Me
NH
(39)

Scheme 55

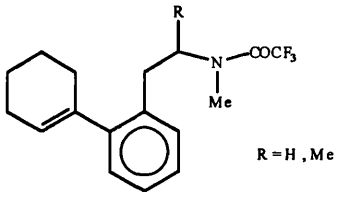
(2.2.) *Results & Discussion.*

Attempted cyclisation of (23) by employing the same type of reaction conditions as used by C.S. Williams[15] with only minor changes led only to N-deacetylation [scheme 55]. No cyclisation products were detected. Decomplexation of the chromium complex (37) was then carried out with $h\nu/O_2$ in Et_2O.

The failure of the metal promoted cyclisation was originally ascribed to the probability that the amine group released under the reaction conditions might interact with the metal first rather than with the alkene system. If this was so then a comparison of the ^1H nmr spectra of the complexed (37) and the uncomplexed (39) amines should show a difference in the δ values of the N-methyl proton signals and also in those of the benzylic resonances. The methyl resonances were not changed, but for (39) the benzylic protons resonate as a singlet whereas in the complex (37) the signals form an AB spin-spin pattern, revealing the non-equivalence of the protons (δ 3.43, δ 3.63; J= 14 Hz). This effect suggests that although these protons are now diastereotropic there is not free rotation about the carbon-nitrogen bond and there may be some interaction with the metal enforcing rigidity into the system.

Failure to cyclise may also reflect that the conjugated styrene unit cannot attain the 109° angle needed for an ideal 6-*endo*-trig reaction profile. For example, the aromatic ring and the double bond of the cyclohexenyl group will adopt a conformation in which the maximum π-electron overlap is attained. Despite the fact that steric interactions between 2'-protons and *ortho*-substituents will not allow total co-planarity between the aromatic and alkene systems, this conjugation will have an effect and prevent the nitrogen atom assuming the required trajectory needed for bonding to the β-carbon of the styrene. We noted, that for steric comparisons, this cyclisation is similar to a disfavoured 5-*endo*-trig [here the rigidity of the three bonds from the benzylic carbon to the alkene is maintained by the sp^2 nature of the aromatic ring] . Homologation of the alkyl chain to that in compound (40) would then bear more similarities to the favoured 6-*endo*-trig.

If this is the explanation for the failure of this reaction then an extension of the α-phenylbenzyl unit in (34) to a β-phenylethyl unit may prove more useful. This homologation can be easily envisaged from (33)[126, 127] via a reduction to the corresponding aldehyde and condensation with nitromethane or nitroethane and subsequent reduction with LAH to produce (40) [scheme 56]. It is also interesting to note that when R = Me compound (40) will contain a chiral centre and further to the relative stereochemistry induced by the chromium, this may influence the absolute stereochemistry in the final product. Although this seemed a plausable line of enquiry to follow we did not as other possibilities came to light.

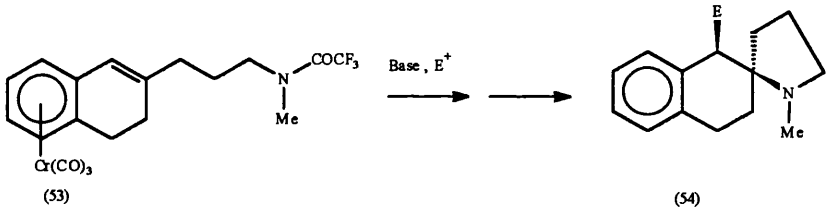


(40)

Scheme 56

(2.2.) 5-*Exo*-trig spirocyclisation

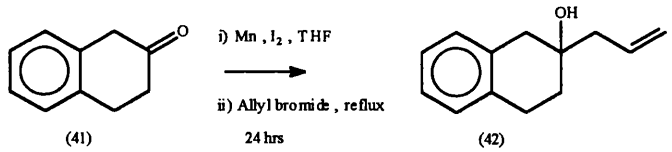
There are two potential reasons for the failure to cyclise (53) . First the adverse geometry of the ring-forming reaction and secondly the possibility that the nitrogen atom of the side chain can interact with the metal. To counteract at least one of these problems we decided to study the ring closure of the complex (53) . Here at least the cyclisation is of the favoured 5-*exo*-trig type. This was anticipated to afford the spirocycle (54), and since there are few literature references for such compounds, we considered that investigation would have additional merit [scheme 57]. Our strategy for the synthesis of the uncomplexed starting material demanded the synthesis of a 2-alkyl-3,4-dihydronaphthalene and we approached this by examining enamine and Wittig procedures based upon tetralones as well as through direct alkylation.



(53) (54)

Scheme 57

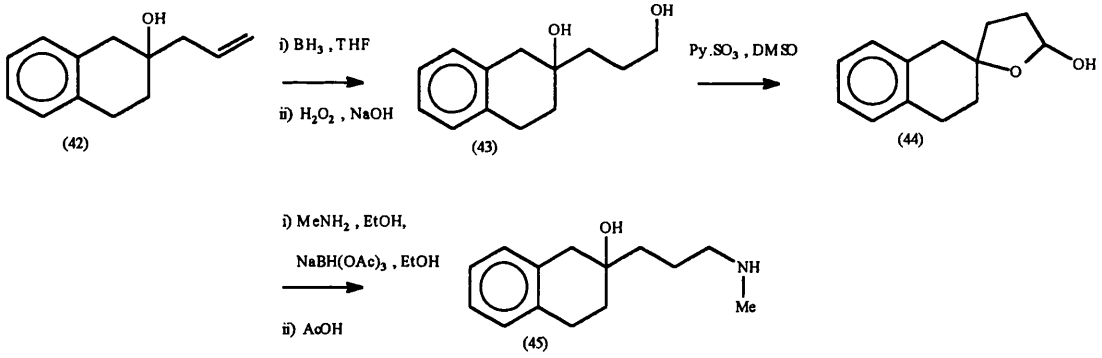
After several unsuccessful attempts to gain entry into α- and β- tetralones via enamine chemistry [100] and Wittig type couplings, alkylation of β-tetralone was effected by the use of a variation of the Grignard reaction mediated by manganese (0) [101]. The use of this reagent was necessary because in the cases where Grignard reagents are reacted with easily enolizable aldehydes or ketones the most prominent reaction is deprotonation (Grignard/carbonyl α-protons)[101]. N.B the last reagent is necessary to minimise enolate formation through enhancing the nucleophilicity of the reagent [124, 125]. In practice the reaction worked well and the desired product (42) was formed in 60% yield [scheme 58].



(41) (42)

Scheme 58

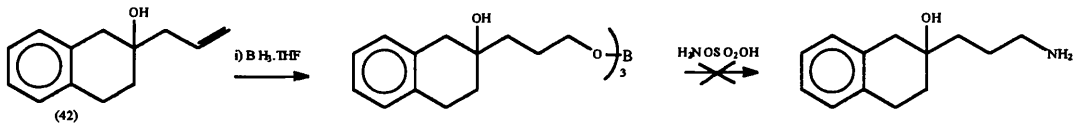
The next step was boronation/oxidation [102] of the side chain in (42); again this was successful and gave the diol (43). Selective oxidation of the 1° over the 3° alcohol group was achieved by use of the mild Swern type reagent pyridine-sulphur trioxide complex in DMSO [103, 104] , but this led to only complex mixtures. It was assumed that one reason for this was the formation of a hemiacetal (44) between the 3° alcohol and the newly formed aldehyde. This could have been an advantage since the product is isomeric with our target, but we failed to isolate the hemiacetal. Instead we attempted to react it *in situ* in a reductive amination procedure with methylamine and sodiumtris(acetoxy) borohydride. The expected product (45) was not obtained and so this route was abandoned [scheme 59].



(42) (43) (44) (45)

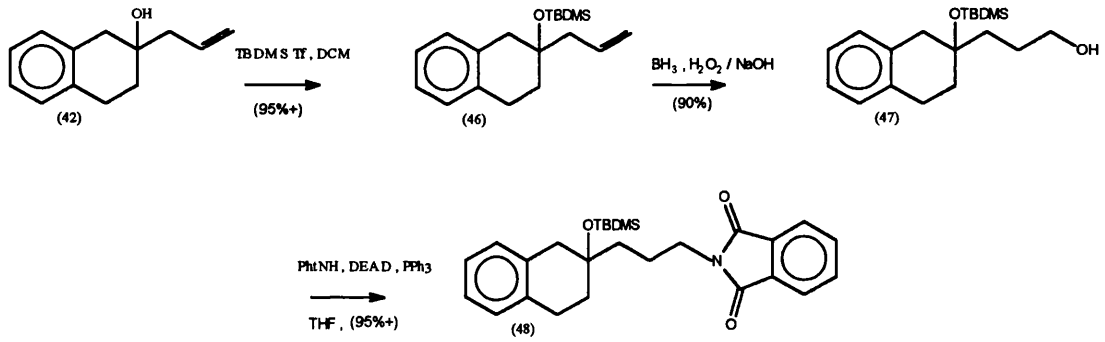
Scheme 59

Next an attempt was made to aminate the double bond of (42) directly by intercepting the initially formed boronate with hydroxylamine-O-sulfonic acid [105] before oxidation. Several attempts at this failed and again we assumed that the problem encountered was due to the presence of the neo-pentyl alcohol [scheme 60].



Scheme 60

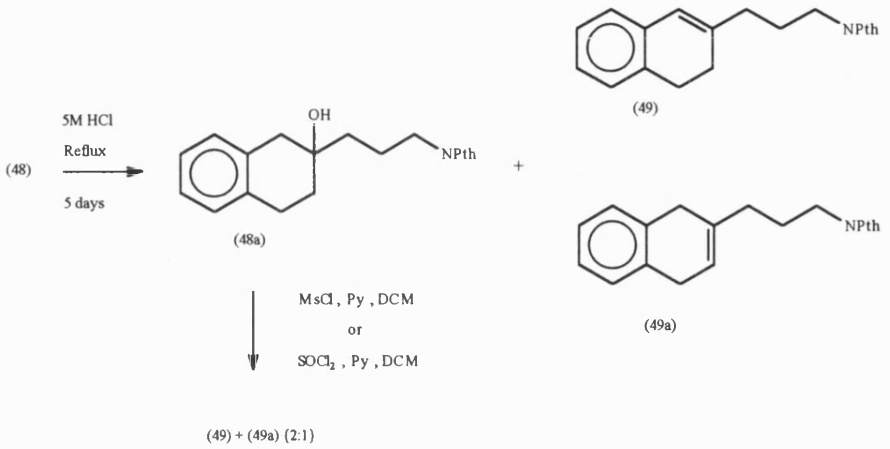
If correct then the obvious step was to protect this hydroxyl group. The choice of protecting group was determined by the conditions envisaged for the rest of the synthesis and after careful consideration a silyl group was selected. Trimethylsilanechloride was discarded as the reagent as the TMSO group is rather sensitive and easily removed, however the tertiarybutyldimethylsilane (TBDMS) unit has extra stability towards acids and has been widely used in synthesis [106]. We used it here and introduced it by reacting the allyl alcohol (42) with the reagents TBDMS-triflate (TBDMS-Tf) and 2,6-lutidine in DCM [107]. This gave a quantitative yield of the ether (46) which was readily converted to the primary alcohol (47). Subsequent replacement of the alcohol with phthalimide under Mitsunobu [108] conditions was successful and gave (48) in very high yield [Scheme 61][109].



Scheme 61

The deprotection/dehydration of (48) to (49) proved much more difficult although treatment with $BF_3.OEt_2$ gave the dihydronaphthalene (49) in 60% yield [110]. Straightforward aqueous acid treatment was unsatisfactory, even treatment with 5M hydrochloric acid in aqueous THF for up to five days at reflux did not complete the deprotection or dehydration. A mixture of starting material, the free

alcohol and the eliminated products (49) and (49a) was produced (with an alkene isomer ratio of the conjugated to the non-conjugated isomer of ~2:1 respectively). The free alcohol (48a) could be easily eliminated by the use of either of the two conditions employed for the similar reactions of (25) to (26) [scheme 62] [96].



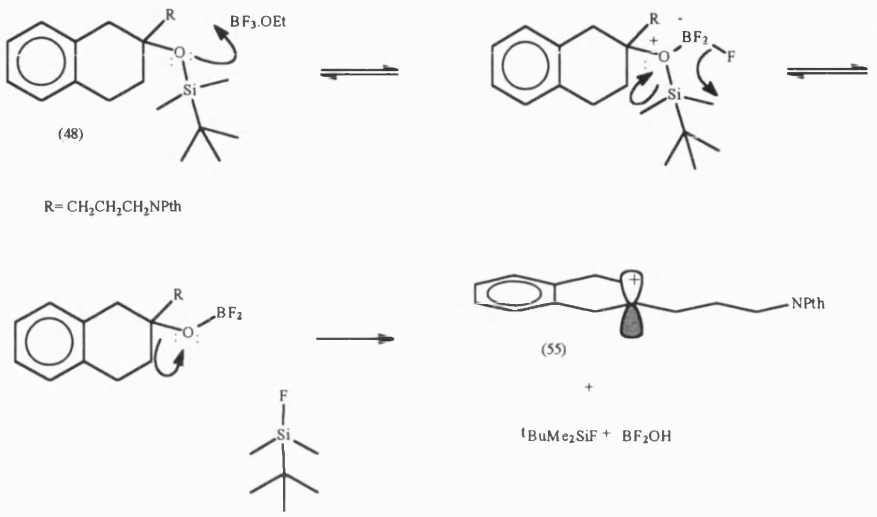
Scheme 62

Interestingly, the isomer ratio of the alkenes produced by either of the three methods above was always the same at ~2:1 (as determined by the relative integrals of the alkenic proton signals in the ^1H NMR spectra). Therfore it is reasonable to suppose that these reactions all proceed through an E1 type mechanism, thus the activation of the alcohol (48a) by protonation or esterification allows the formation of the tertiary homobenzylic cation (55) [scheme 63]. Elimination of a benzylic proton would be preferred over one from C-3 and this is reflected in the product ratio.

The 3° homobenzylic cation (55)

Scheme 63

When (48) was treated with $BF_3.OEt_2$ [110] in DCM, the TBDMS group was immediately lost and both alkenes were formed, but, with time complete conversion into the conjugated isomer (49) was effected. The minimum time required for the complete conversion is about 48 hrs at room temperature. The deprotection of the alcohol is believed to occur through the mechanism shown below [110] [scheme 64].

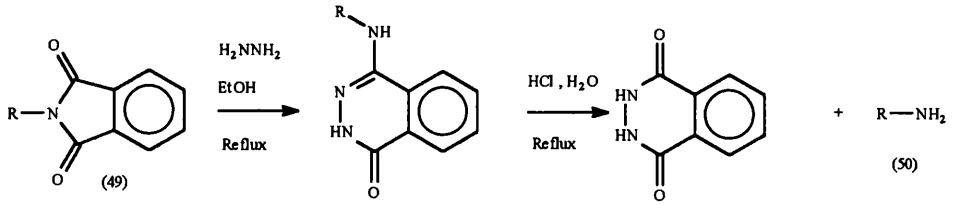


De-silylation by borontriflouride

Scheme 64

The deprotection step needs a minimum of 0.25 mol equivalents of Lewis acid, but the conversion to (49) is effected by only a catalytic quantity of BF_3 etherate . Interestingly if moisture is vigorously excluded the isomerisation fails, suggesting that protonation is necessary, recycling the tertiary cation and eventually giving the thermodynamically favoured product.

Ring opening of the phthalimide (49) with hydrazine [111] proved to be straightforward . There are two distinct steps involved in this deprotection, as shown below. The driving force being the generation of a 6 rather than a 5 membered fused-aromatic ring. The ring-expanded intermediate was hydrolysed without isolation and gave the free amine (50) in near quantitative yield [scheme 65].



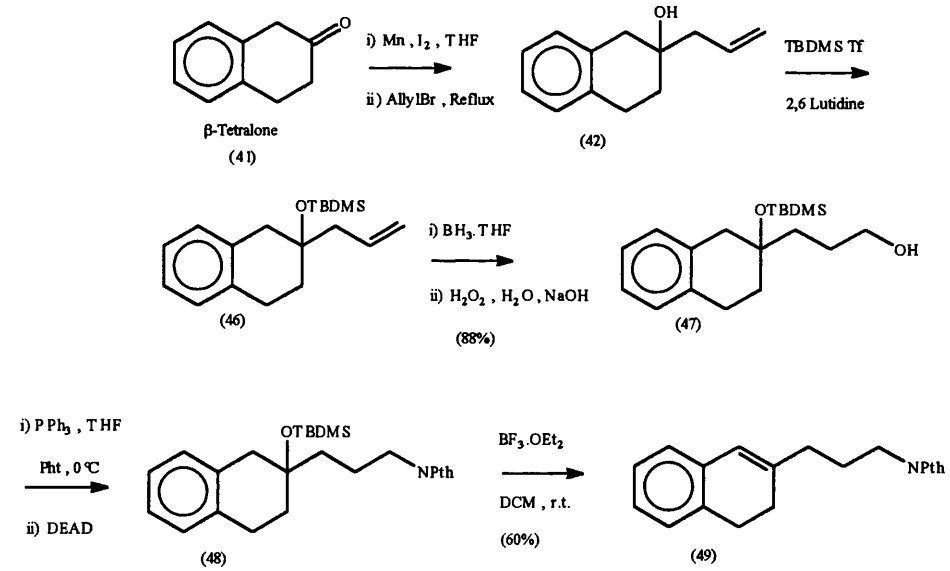
Phthalimide Hydrolysis

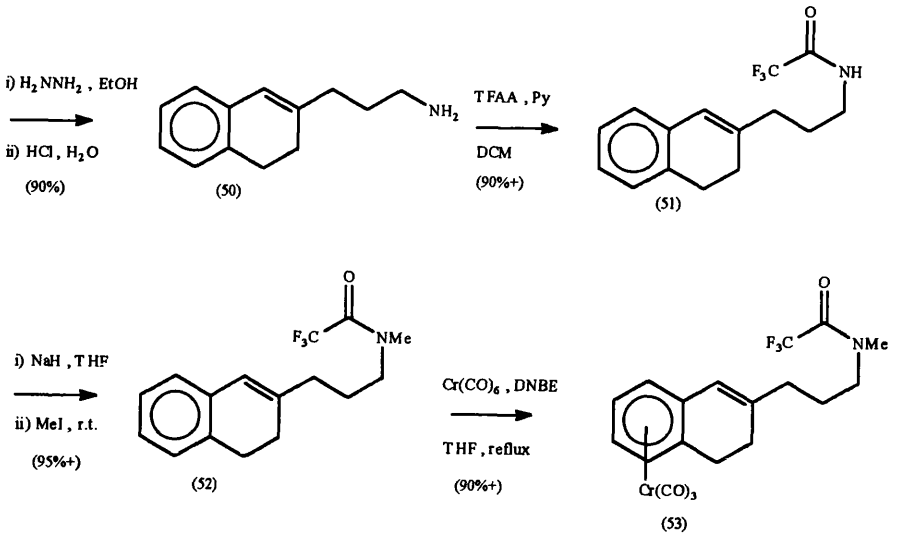
Scheme 65

Subsequent protection of the amine (50) as the trifluoroacetyl derivative and then N-methylation by standard chemistry gave (52).

Complexation of (52) with chromium hexacarbonyl generated the required compound (53) in exceptionally high yield (90%).

The complete synthesis of (53) from (41) is summarised below [scheme 66].



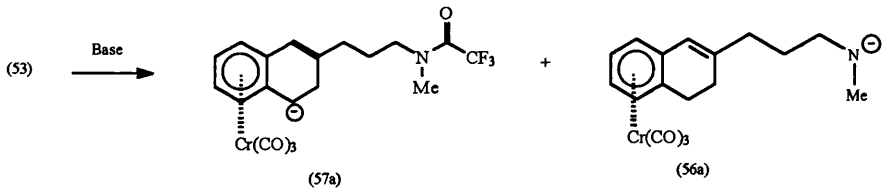

i) H_2NNH_2 , EtOH
ii) HCl , H_2O
(90%)
(50)
TFAA , Py
DCM
(90%+)
(51)
i) NaH , THF
ii) MeI , r.t.
(95%+)
(52)
$Cr(CO)_6$, DNBE
THF , reflux
(90%+)
(53)

Scheme 66

(2.4.) **Results and Discussion.**

Attempted cyclisation of (53) under the mild basic conditions ($NaHCO_3$/methanol/H_2O) previously used successfully by C.S.Williams[1] gave only the hydrolysed product (56). Variations of the conditions such as the use of biphasic solvent systems (chloroform or DCM/H_2O) but with the same base simply returned the complexed amine (56). Attempts to cyclise this compound itself in contact with catalytic amounts of sodium methoxide also failed.

Similarly reaction of the metallated amide (53) with methyl lithium and attempts to capture the expected cyclised carbanion with either diphenyldisulfide or benzaldehyde did not lead to new products. Partial deprotection rather than complete loss of the trifluoroacetamide unit occurred and the amide (53) and the amine (56) were returned. The purity of the methyl lithium was carefully checked before this work thus we are very surprised at this lack of reactivity. One possibility seemed to be that the known reaction between Grignard reagents and the CO ligands takes place instead [53]. This would remove both reagents from the reaction sphere and consequently give the impression that the amide had partially reacted or, that preferential deprotonation at the benzylic position occurred leading to the carbanion (57) [scheme 67].



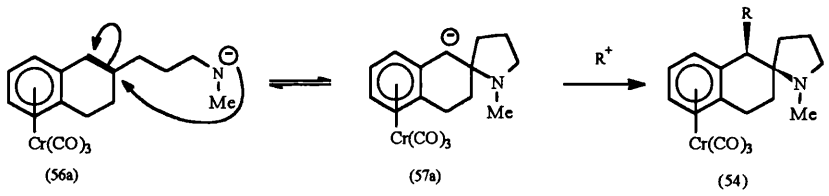
Scheme 67

Based on the assumption that benzylic deprotonation might be taking place several bases were used and electrophilies were added in the hope that benzylic substitution might be detected. Table 2 gives the bases and conditions used.

Entry	Base	Electrophile	Conditions	Reagent
1	**MeLi**	**MeSSMe**	**-78°C , THF**	**(53)**
2	**MeLi**	**PhCHO**	**-78°C , R.T.**	**(53)**
3	**MeLi**	**$NH_4Cl_{(aq)}$**	**-78°C - 0°C, THF , DMPU**	**(53)**
4	**MeLi**	**PhSSPh**	**-78°C - 0°C, THF**	**(53)**
5	**MeLi**	**MeI**	**-10°C -R.T. , THF**	**(53)**
6	**MeLi**	**MeI**	**-78°C , Et_2O**	**(53)**
7	**MeLi**	**MeI**	**0°C , Et_2O**	**(53)**
8	**LDA**	**MeI**	**-78°C , THF**	**(53)**
9	**LDA**	**MeSSMe**	**-78°C - 0°C , THF**	**(53)**
10	**LDA**	**MeI**	**0°C , THF , DMPU**	**(53)**
11	**LDA**	**MeI**	**-78°C , THF ,**	**(53)**
12	**LDA**	**D_2O**	**-78°C , THF**	**(53)**

Table 2

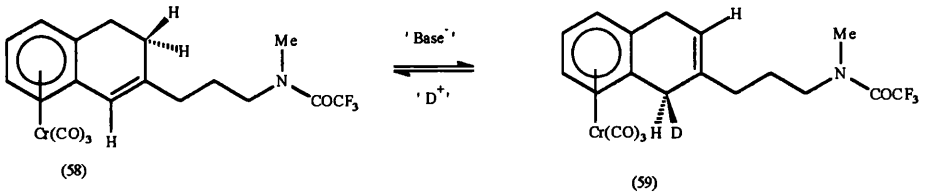
Entries 1, 2, 4, and 9 as well as investigating benzylic deprotonation were also designed to intercept any equilibration which could proceed from the expected cyclisation shown in scheme 68.



Scheme 68

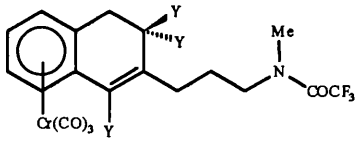
Unfortunately neither cyclisation nor benzylic substitution products were detected from any of the reactions listed in table 2. Surprisingly even the attempted incorporation of deuterium at the benzylic

or the pre-alkenic site failed. The possibility of base promoted isomerisation (58) ⇔ (59) [scheme 69] would also be detectable by deuteration but this was not substantiated.



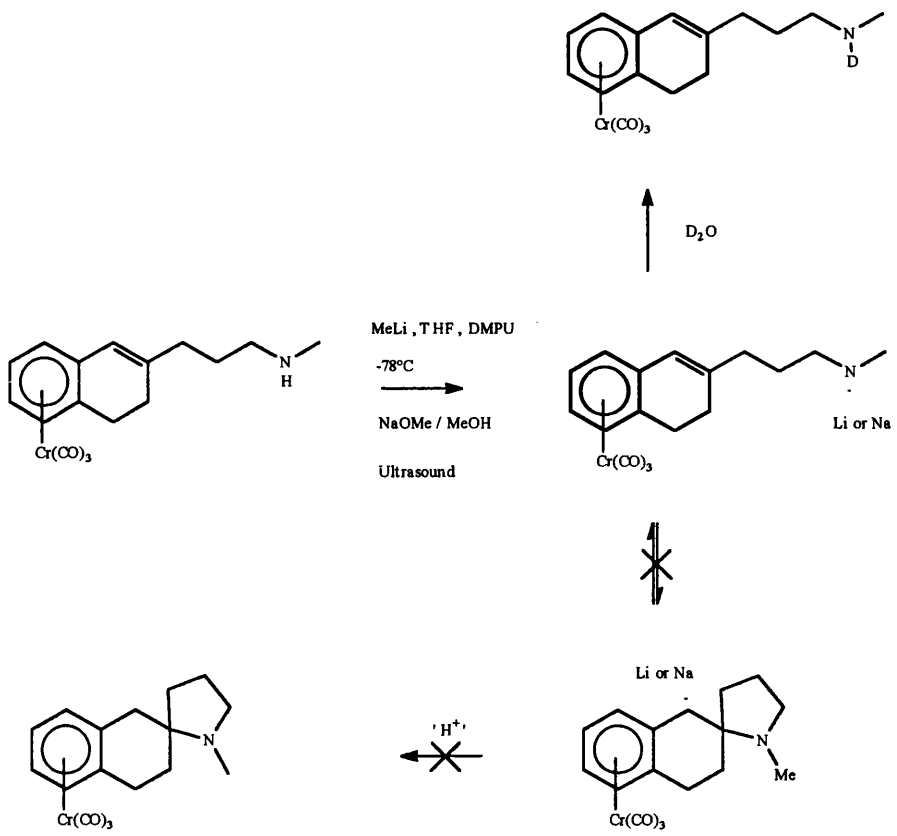
(58) (59)

This would eventually lead to the incorporation of deuterium into sites Y



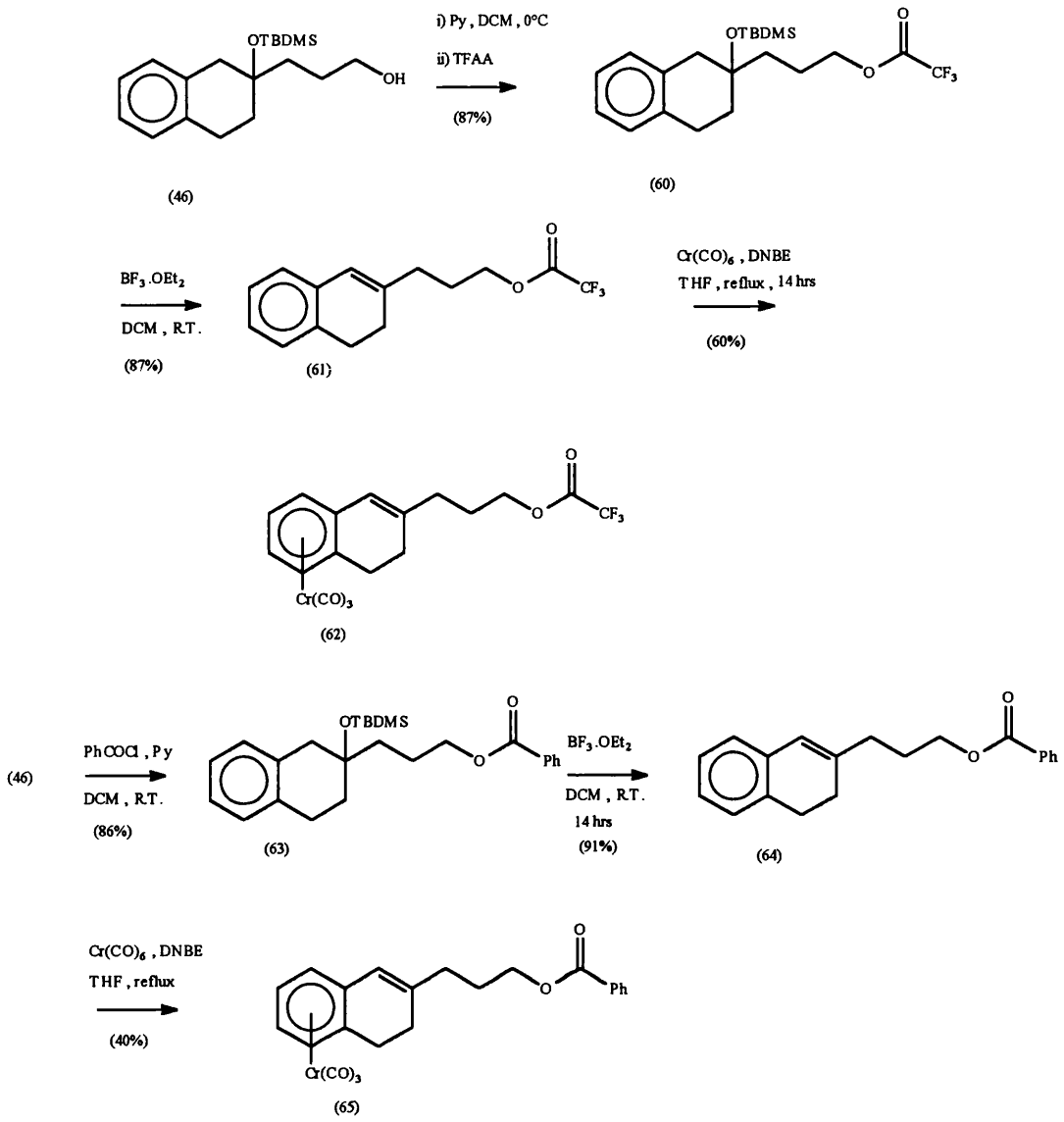
Scheme 69

Bearing these results in mind we tried to effect cyclisation via the production of stronger nitrogen anions. Treatment of the amine (56), a product from most of the failed cyclisations, with sodium methoxide in methanol, ultrasound or methyl lithium at -78°C in THF and DMPU as a co-solvent generated the anion but in neither case were cyclisation products formed. Instead, quenching of the reaction mixture with D_2O did produce the free amine deuterated at nitrogen [scheme 70].



Scheme 70

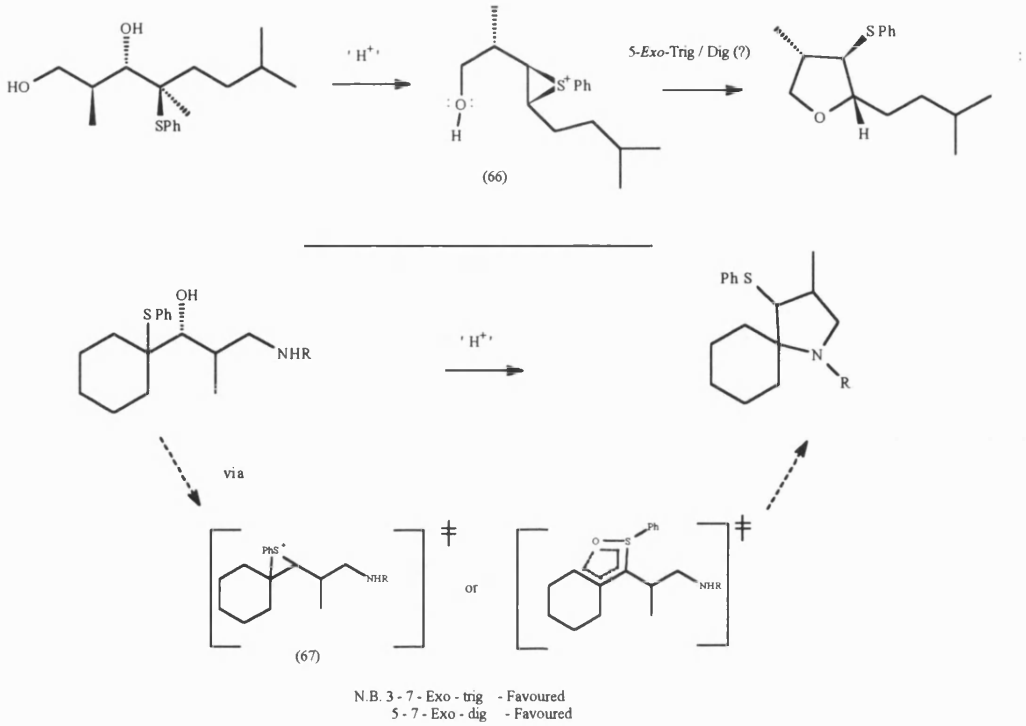
Thus no successful reaction was achieved and purely as an extension to this work the oxygen derivatives of (53) were prepared, as shown in scheme 71, to test the possibility that the "harder" oxygen nucleophile might produce some unexpected results[128, 129].



Scheme 71

The synthesis of the two esters (61) and (64) was accomplished without difficulty from the alcohol (46) and each was then concerted into it's η^6–chromium tricarbonyl complex. We anticipated that on hydrolysis the corresponding alcohols might cyclise *in situ* to a spiro ether.

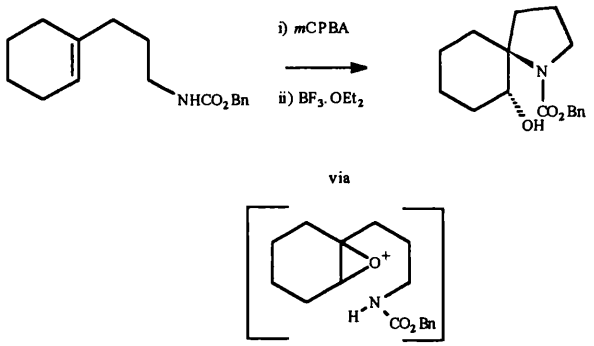
There is some precedent for the formation of cyclic ethers along similar lines, see for example the work of S.Warren *et al.* [112a-d], who showed that the sulfenium cations (66) and (67) cyclise to the corresponding furans by a 5-*exo*-trig process. In this case however nitrogen nucleophiles are equally effective and this caused us some concern [scheme 72].



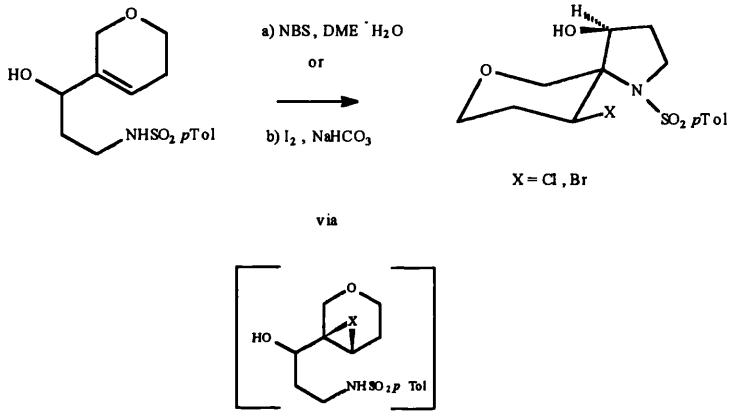
Scheme 72

Indeed in our work the two oxygen derivatives (62) and (65) proved to be exceptionally sensitive compounds and were prone to decomplexation and deprotection (of the alcohol). Even with these logistical problems in prospect both were subjected to aqueous basic conditions with or without ultrasound but disappointingly no cyclisation products were formed.

At this point we decided to look more closely at our failed cyclisation reactions. Molecular modelling of the 5-*exo*-trig substrate shows that the ideal 109° approach of the incoming nucleophile demands a very constrained array of the methylene units in the side chain nucleophile. In general examples where 5-*exo*-trig spirocyclisations occur they show the probable involvement of the concomitant ring opening of a three membered ring mediated by a Lewis acid [scheme 73 and 74].



Scheme 73

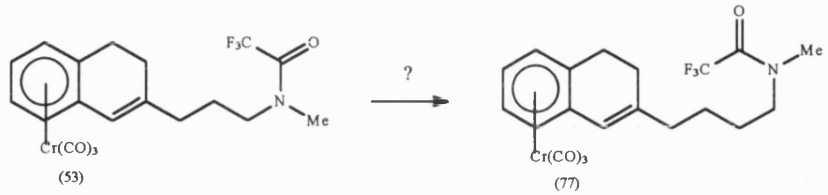


Scheme 74

This would ensure the participation of a carbocationic centre, rather than an anion simply stabilised by delocalisation. In order to make our system more competitive we next decided to extend the number of methylene units in the side chain by one. This would relieve strain in the transition state in cyclisation yet still be an allowed (6-*exo*-trig) reaction.

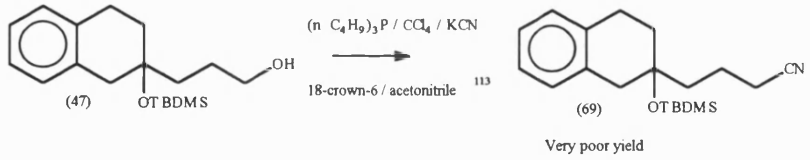
(2.5.) 6-*Exo*-trig-spirocyclisation

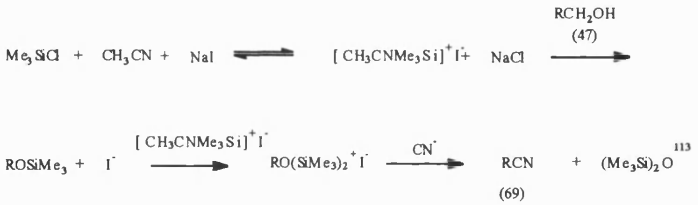
The homologation of (53) to (77) [scheme 75] was originally expected to pivot around the intermediate (47) [scheme 76].



Scheme 75

In principle the alcohol could be converted directly to give the nitrile (69) by treatment with tributylphosphine/carbon tetrachloride and potassium cyanide in the presence of 18-crown-6. Although there is literature precedent [113] for a similar transformation in practice this compound failed to give (69) in a reasonable yield. It also failed to react with the trimethylsilyl chloride/acetonitrile/sodium iodide/potassium cyanide reagent system [Scheme 76] [113].





Scheme 76

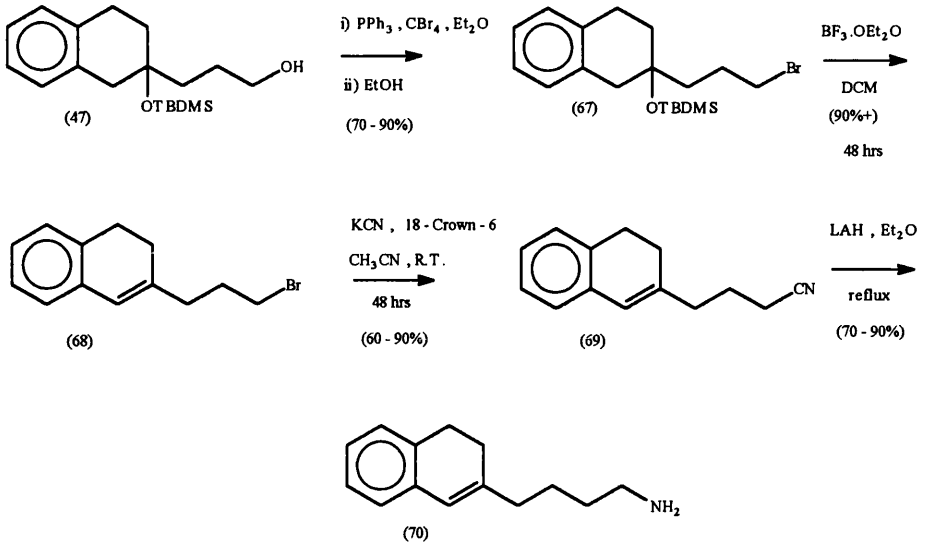
Since we had already formed the o-trifluoroacetyl derivative of (47) we attempted nucleophilic substitution reactions with cyanide ion [114] upon this substrate under various conditions. All of these

failed. Frustrated by these disappointing results we tried to carry out a substitution reaction on the acetate with the anion of nitromethane. Again no reaction occurred.

We have no coherent reason other than steric effects to account for the durability of the alcohol and it's acetate, which were returned either hydrolysed or unchanged. Cyanide ion replacement of bromine atoms bonded at primary and secondary saturated alkyl centres has been used for a long time in synthesis, thus we sought to synthesise the bromide (67). Anti Markownikov bromination of the terminal alkene (46) using borane, bromine and sodium methoxide [115] proved to work but the yield was low and variable (30 - 60%). With this in mind direct replacement of the hydroxyl of the alcohol (47) by bromine [93] was attempted.

Indeed conversion of the alcohol (47) into the bromine compound (67) [93] was achieved in up to near quantitative yield. The corresponding chloride derivative (97) was prepared by treatment of (47) with $SOCl_2$ in pyridine. Rather than attempting the functional group conversion at this stage compounds (47a) and (67) were then treated with borontrifluoride etherate to generate the dihydronaphthalenes (e.g. 68). Each compound was then reacted with cyanide ion as outlined in scheme 77. The bromo derivative proved to be superior over the chloro compound in both steps and gave better yields [91, 116] thus the bromo derivative was used.

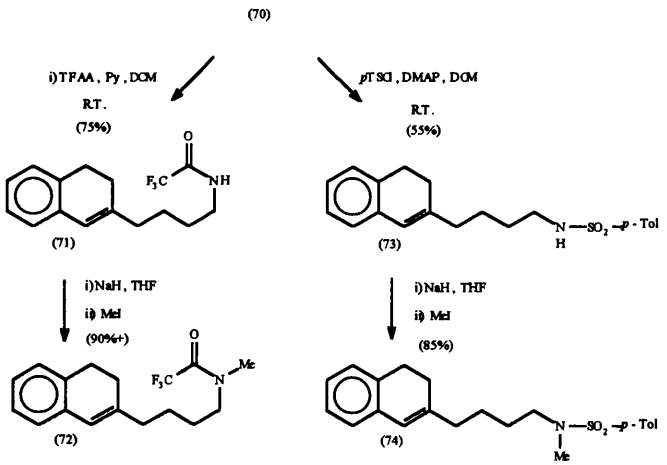
Compounds (47a) and (67) as choices for synthesis



Scheme 77

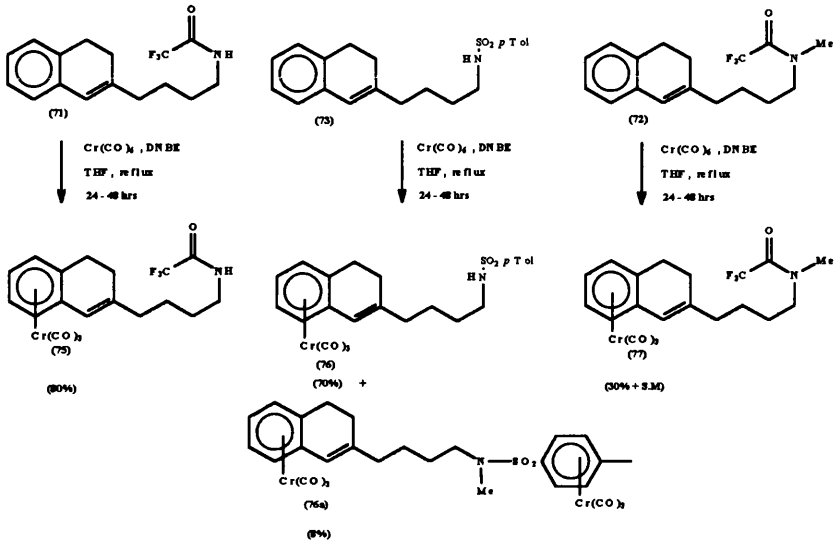
Finally the reduction of the nitrile was carried out by treating it with LAH giving the amine (70) in good yield. Thus it was converted into the N-trifluoroacetamide (71) and the N-methyl derivative (72) plus the tosylamide (73) and its methyl derivative (74) as shown in scheme 78.

This provided a series of compounds for complexation and attempted cyclisation.



Scheme 78

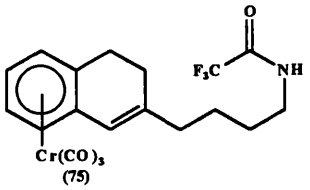
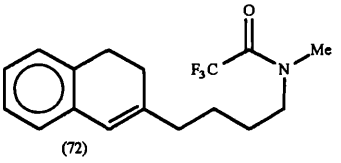
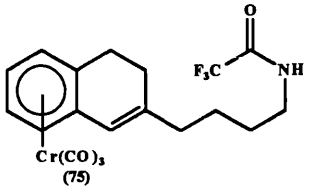
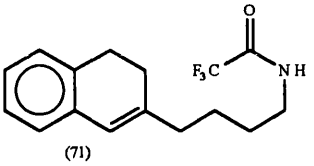
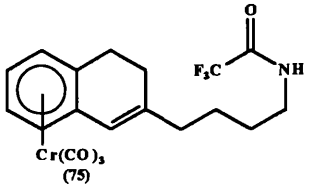
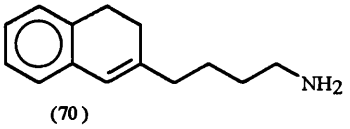
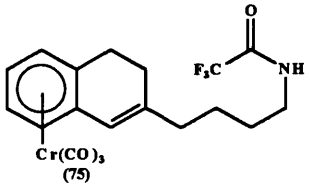
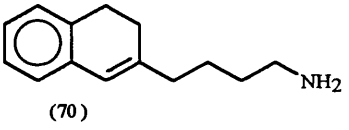
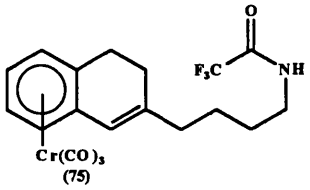
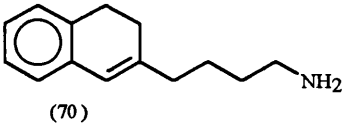
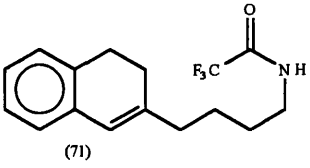
Chromination of compounds 71, 72, 73 and 74 were carried out under Mauffey-Pauson conditions to generate the tricarbonyl compounds, all in reasonable yield. The reduced electron density of the aromatic ring in the *para* toluene ring of (73) led to the selective mono-chromination of the naphthalene ring in good yield (70%) and the di-chrominated product (74) as a minor product [scheme 79].

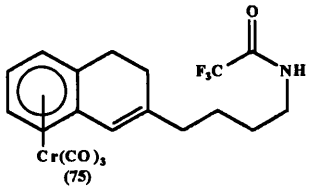
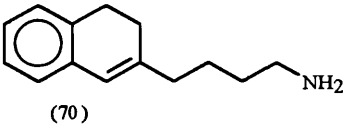
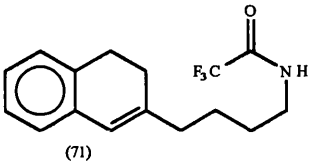
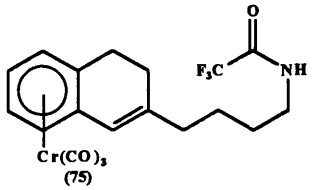
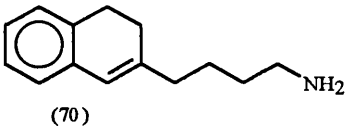
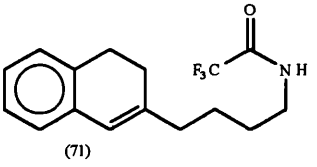
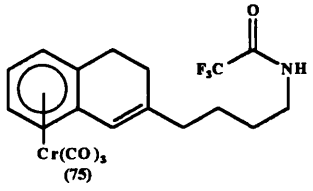
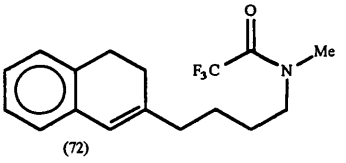
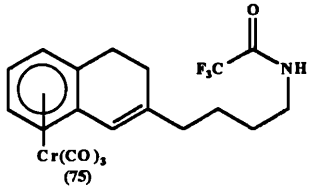
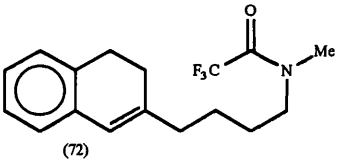
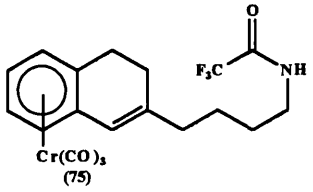
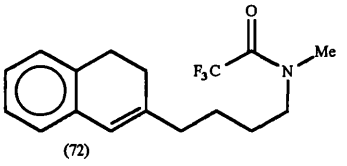


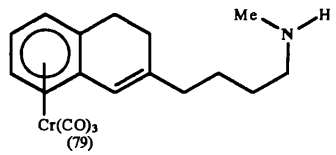
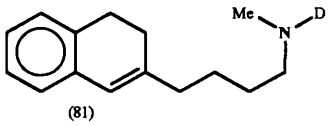
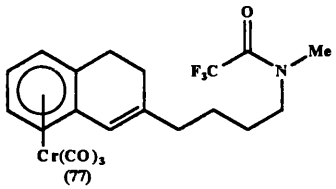
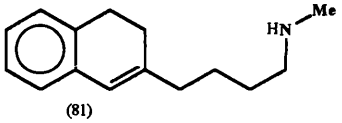
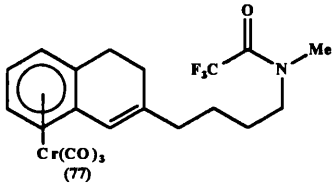
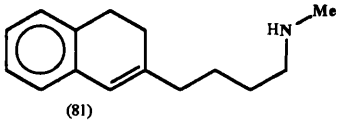
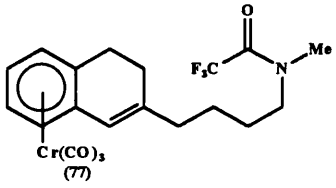
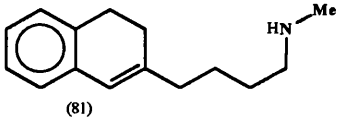
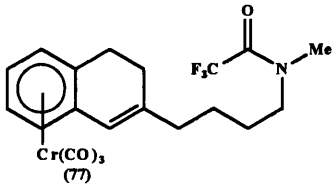
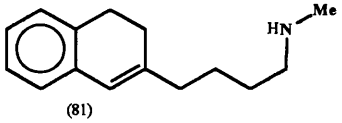
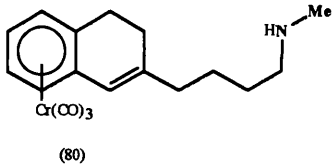
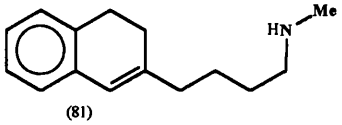
Scheme 79

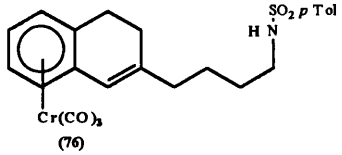
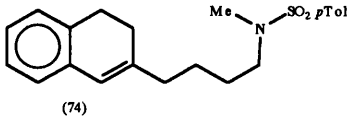
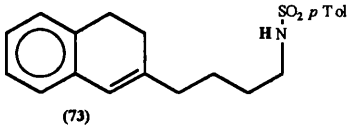
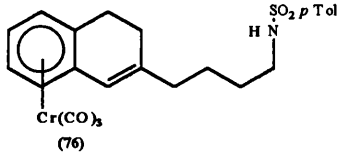
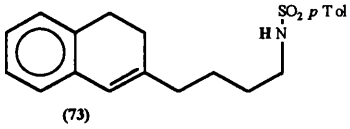
Table 3 shows the variety of conditions used in attempts to cyclise the complexes 75, 76, 77 and 79. Sadly none of these effected the desired reactions, rather N - methylation and hydrolysis were observed.

Table 3

Substrate	*Conditions*	*Products*
 (75)	i) MeLi , -78°C , THF ii) MeI , -78°C - R.T. iii) hν/O_2 , Et_2O	 (72)
 (75)	i) I_2 , DCM , 0°C ii) hν/O_2 , Et_2O	 (71)
 (75)	i) K_2CO_3 , MeOH , H_2O , ultrasound , 72 hrs ii) hν/O_2 , Et_2O	 (70)
 (75)	i) K_2CO_3 , MeOH , H_2O , Me_2S_2 , ultrasound , 72 hrs ii) hν/O_2 , Et_2O	 (70)
 (75)	i) NaHMDS , THF , -78°C iii) hν/O_2 , Et_2O	 (70) 10%  (71) 90%

 (75)	i) KHMDS , THF , -78°C ii) hν/O_2 , Et_2O	 (70) 12%  (71) 88%
 (75)	i) KHMDS , THF , DMPU , -78°C ii) hν/O_2 , Et_2O	 (70) 10%  (71) 90%
 (75)	i) NaHMDS , THF , -78°C ii) MeI , -78°C - R.T. iii) hν/O_2 , Et_2O	 (72) (32%)
 (75)	i) NaHMDS , THF , DMPU , -78°C ii) MeI , -78°C - R.T. iii) hν/O_2 , Et_2O	 (72) (47%)
 (75)	i) NaH , 0°C, THF ii) MeI , 0°C iii) hν/O_2 , Et_2O	 (72)

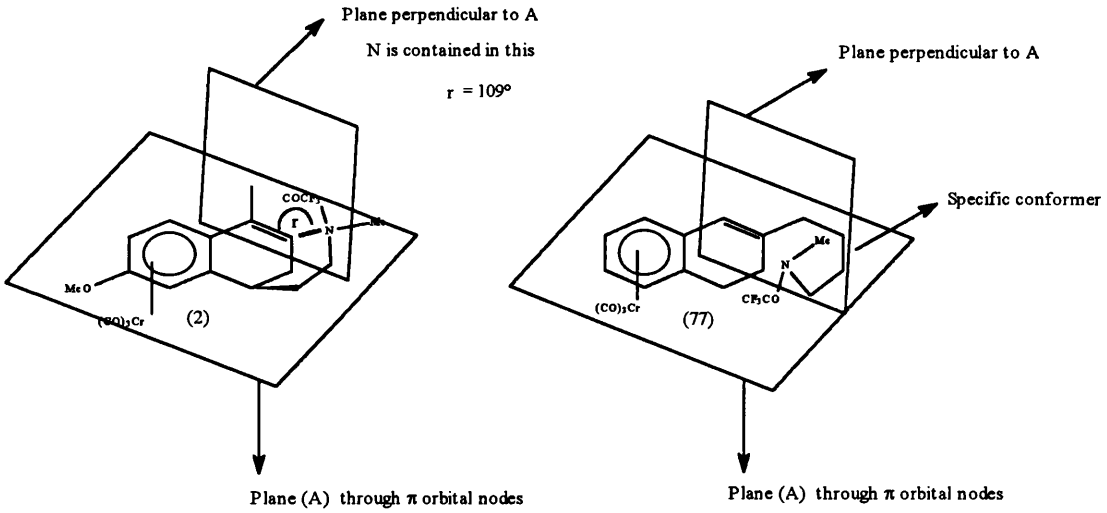
 (79) Generated from (77)	**i) MeLi , -78°C , THF** **ii) DMPU , R.T.** **iii) D_2O** **iv) hν/O_2 , Et_2O**	 (81) **(65%)**
 (77)	**i) K_2CO_3 , MeOH , H_2O ,** **ultrasound , 72 hrs** **ii) hν/O_2 , Et_2O**	 (81)
 (77)	**i) K_2CO_3 , MeOH , H_2O ,** **Me_2S_2 , ultrasound , 72 hrs** **ii) hν/O_2 , Et_2O**	 (81)
 (77)	**i) K_2CO_3 , MeOH , H_2O ,** **PhCHO , ultrasound , 72 hrs** **ii) hν/O_2 , Et_2O**	 (81)
 (77)	**i) MeLi , -78°C** **ii) DMPU , - R.T.** **iii) hν/O_2 , Et_2O**	 (81)
 (80)	**i) NaHMDS , THF , DMPU ,** **-78°C** **ii) H_20** **iii) hν/O_2 , Et_2O**	 (81)

 (76)	i) KH , DMPU , THF , -78°C ii) MeI iii) hν/O_2 , Et_2O	 (74) (20%)  (73) (80%)
 (76)	i) K_2CO_3 , MeOH , H_2O , ultrasound , 72 hrs ii) hν/O_2 , Et_2O	 (73)

The initial reactions carried out with aqueous base were unsuccessful and so we attempted to capture any equilibration products that may exist by adding an electrophilic quenching agent that would form strong bonds with carbon and not with nitrogen (i.e. X-S bonds generated from Me_2S_2) and reagents that react reversibly with nitrogen and not with carbon (i.e. benzaldehyde). Again we failed and results from these experiments were very disappointing. Next we decided to ensure that the anionic centre in the side chain of each complex was fully developed rather than inferring its generation through hydrolysis of the amidic bond. Treatment of the NH compounds with MeLi, sodium hydride, potassium or lithium hexamethyldisiylazide did produce the anion as can be seen from the fact that the addition of with methyl iodide to the reaction mixtures gave N-methyl derivatives, but again no cyclisation was noted. Increased solvation of the anion by the use of DMPU [117] (a replacement for HMPA because of its hazardous nature) which is known to improve the yield and rate of reaction in addition of anions to arene chromiumtricarbonyl derivatives [50] had no effect, except it's presence increased the extent of N-methylation.

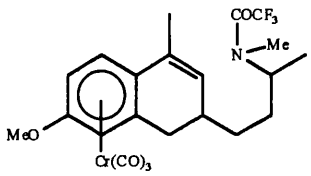
Clearly our choice of reactants is inappropriate and it seems very unlikely that our failures are due to misapplied techniques. However molecular modelling of our substrates showed that the nucleophilic termini of the side chains can reach the correct position for entry to the double bond in each case. Thus, despite the fact that potentially high energy conformers may be necessary there appears to be no steric or serious energetic reason for the lack of reaction.

From an analysis of the structure of the successful cyclisation substrate (2) and (77), several conclusions were reached. Firstly the position of the nitrogen nucleophile in (2) with respect to the double bond is such that the ideal 109° angle of approach is nearly always available to it. There is a large degree of flexibility and the nucleophile can also be available in the plane perpendicular to the arene π-orbitals. This is not the case for (77) and as can be seen in scheme 79 the nucleophile is not contained within the plane perpendicular to the π-orbitals to such a degree.



Scheme 79

As time was now getting short we embarked upon the synthesis of compound (92) as this now held a very close resemblance to (2). Spirocyclisation is not now an issue, and the nucleophile is held in much the same position as the reactive substrate. In addition a *para*-methoxy group is present in the aromatic nucleus, this was not the case in the earlier compounds. Indeed the *para*-methoxy group has been shown to have beneficial effects on chromium complexation (higher electron density in the ring)[118] , although it is not easy to see why the presence of such a group could favourably influence the cyclisation reaction (quite the reverse in fact!).

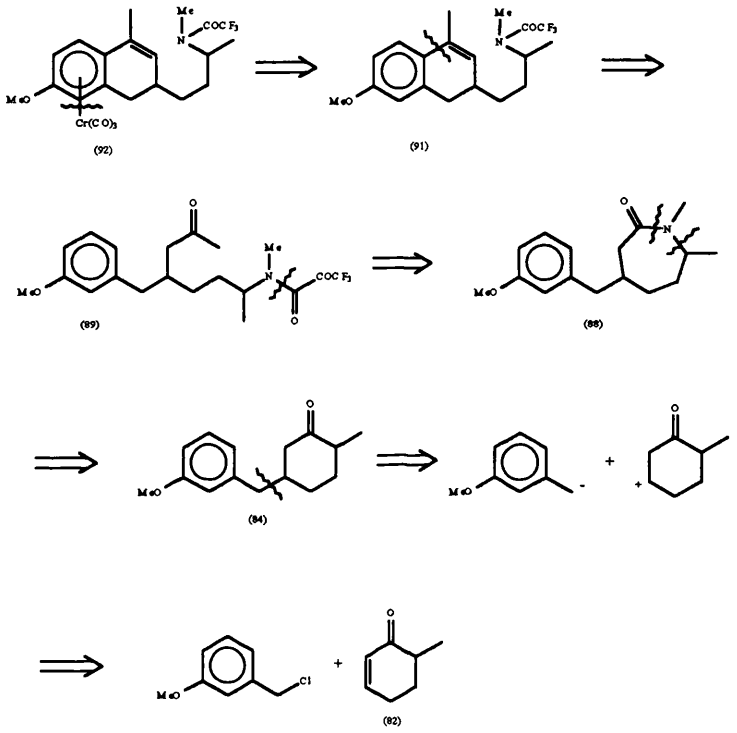


Compound (92)

(2.6) **6-*Exo*-trig-cyclisation**

Synthesis:

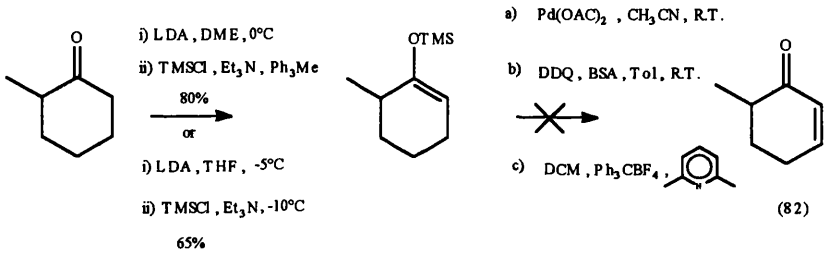
Retro synthetic analysis of the target compound (92) is as follows:-



Scheme 80

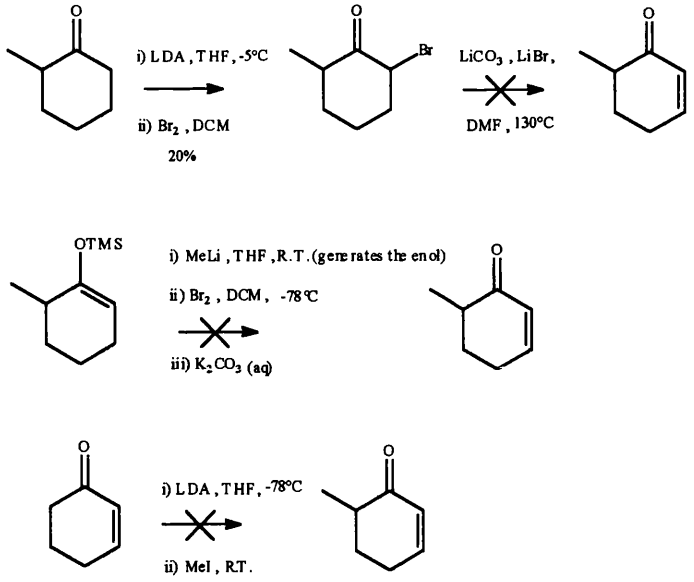
Precedents have been set for the first four steps above [1, 15] and the coupling of 3-methoxybenzyl chloride with 2-methylcyclohex-5-en-1-one follows a 1,4 Michael addition pathway.

Synthesis of the enone (82) was originally approached *via* the TMS ether of 2-methylcyclohexanone [119, 120], produced from its kinetic anion generated by LDA treatment of the ketone at low temperature. Deprotection and oxidation of the conjugate addition product by a variety of reagents is said to give (82) in excellent yields [119, 120, 121]. In our hands these procedures failed and gave only black polymeric by-products. Below is a summation of the failed reactions [scheme 81].



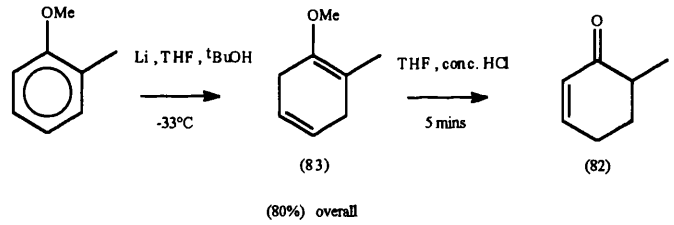
Scheme 81

α–Bromination of 2-methylcyclohexanone and then dehydrobromination with potassium carbonate in DMF is claimed to be successful in forming (82) but again we were unsuccessful in repeating this work. We attempted a slight variation of this procedure and tried to brominate the free enol, from the TMS ether, prior to a dehydrobromination reaction. Deprotection and bromination gave only complex products. Finally treatment of cyclohexenone with LDA at -78°C and subsequent quenching with methyl iodide, also failed [scheme 82].



Scheme 82

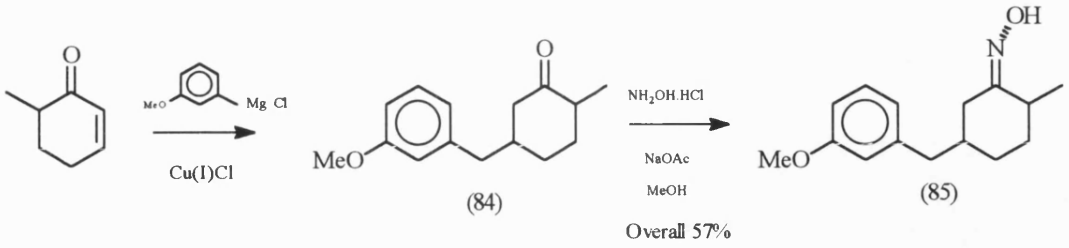
Much effort was expended on these reactions but without a profitable return. However (82) was ultimately synthesised through Birch reduction of 3-methylanisole in the presence of ^{t}BuOH and THF. This produced the thermodynamic 1,4 diene (83), which on acid hydrolysis gave (82) [122] [scheme 83] in excellent yield[130, 131] (80% for two steps).



Scheme 83

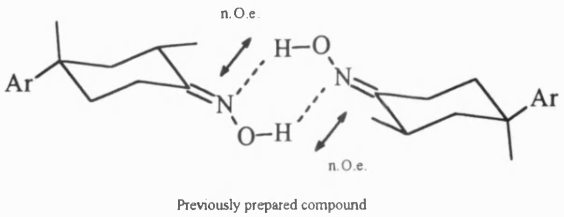
Coupling of (82) with the Grignard reagent prepared from 3-methoxybenzylchloride with a 10% mol equivalent of Cu(I)Cl gave the 1,4 addition product (84) in high yield [91]. The actual yield was not recorded as complete purification of (84) was not carried out due to its sensitivity to oxidation. Partial

purification and then reaction of (84) with hydroxylamine hydrochloride produced the hydroxylamine (85) [1, 15]. The overall yield of (85) from (82) was 57%.



The preparation of compounds (84) and (85)

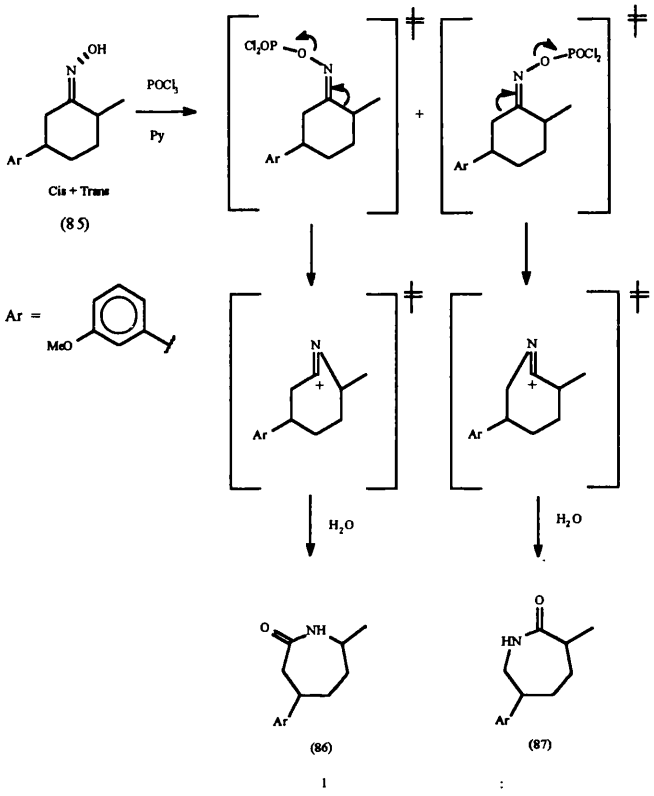
The hydroxylamine (85) exists in both the *cis* (E) and *trans* (Z) forms with the *trans* isomer being favoured thermodynamically. Crystallisation from the pure mixture of (85-E) and (85-Z) gave a solid of m.p. 102°C. The ^{1}H and ^{13}C spectra of which was fully in accord with a single isomer. N.O.e studies confirmed our assumption that this was the trans isomer. Surprisingly this compound did not show an n.O.e. between the resonance of the hydroxyl and that of any other proton. When a similar compound was prepared [1, 15] it existed in a dimeric form in solution as shown in scheme 84 with detectable n.O.e.'s between the hydroxyl and the equatorial methyl hydrogen resonances.



Previously prepared compound

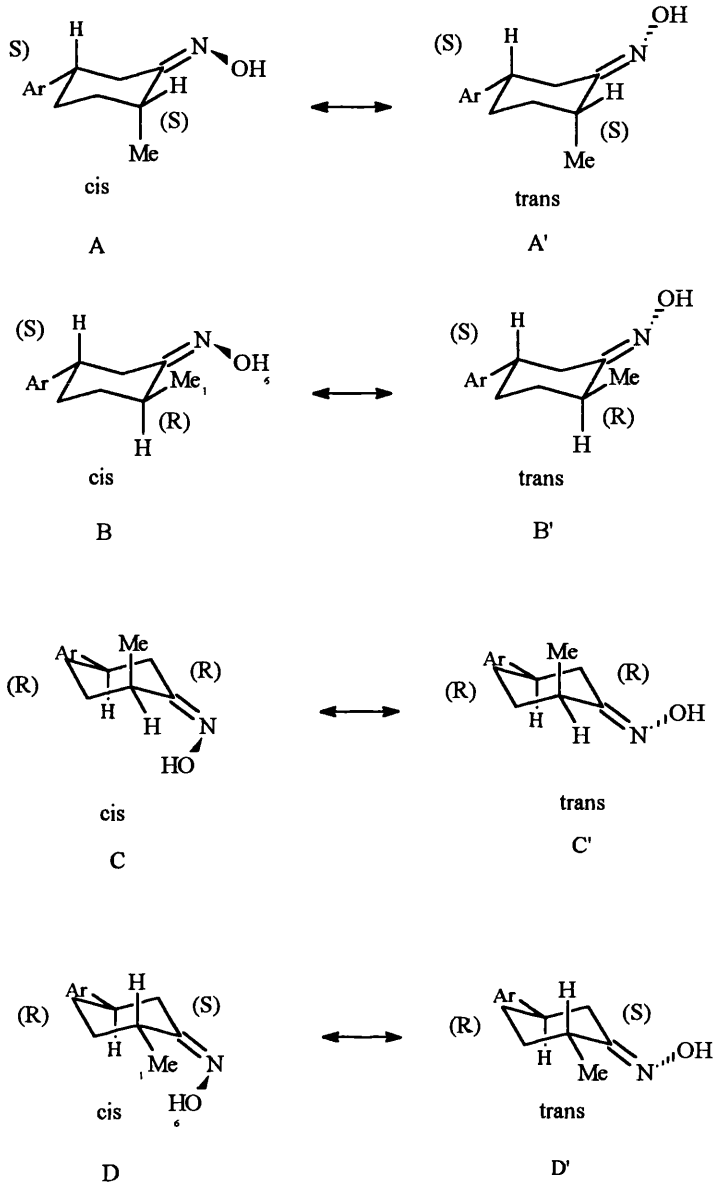
Scheme 84

Ring expansion of the mixed isomers of (85) by treating it with $POCl_3$ in pyridine [116] gave two lactams (86) and (87) in a 18:52 ratio with an overall yield of 65% [scheme 85].



Scheme 85

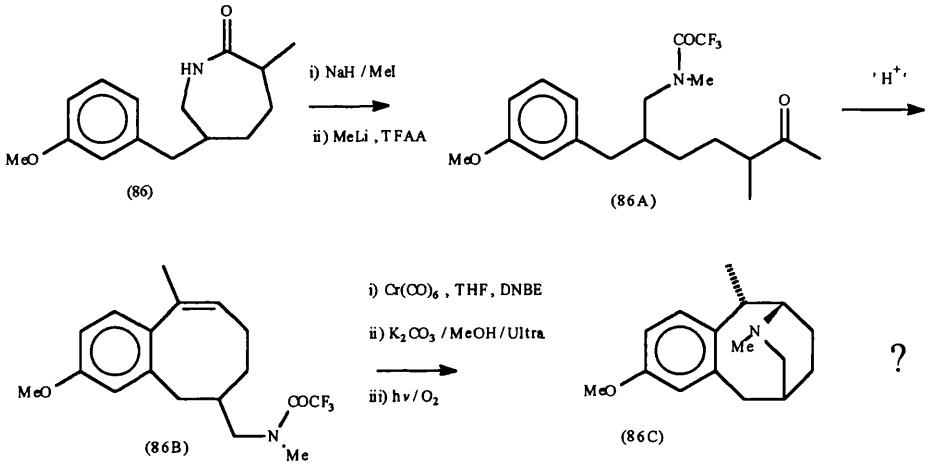
Here it is interesting to note the reason why the ratio of compounds (86) and (87) is 18:52. As the synthesis is "racemic" we created compound (85) in all four diastereomeric forms, of which there are two enantiomeric pairs. If all four cyclohexane diastereoisomers are drawn out fully with the only restraint being that the large aromatic group be equatorial in each, only four conformers of (86) are predicted each having either a cis or trans arrangement of the functional groups. By reference to scheme 86 it can be seen that for the structures that contain the cyclohexane methyl substituent axial (A and C) there is no preference for either the *cis* or *trans* forms (A *vs.* A' or C *vs.* C'). For structures B and D the expected 1,6 steric interactions will favour the *trans* forms in both cases (B' > B and D' > D). Overall this predicts the *trans* isomers to predominate even disregarding the size of the 1,6 interaction and any small preferences in either of the A or C structures. This is indeed borne out in practice.



Scheme 86

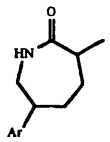
The subsequent separation of the two isomers (86) and (87) proved difficult. Chromatography was only partially successful and for complete purification fractional crystallisation was needed. This was a long repetitive process that eventually led to a very pure product. X-Ray crystallography of both compounds was required to fully prove the assignment of stereochemistry. This together with ^{1}H spectra allowed the relative and absolute stereochemistry to be defined for both (86) and (87).

Although compound (86) could be used as outlined in scheme (87) [1, 15] it was discarded and compound (87) was carried through into the main synthesis.



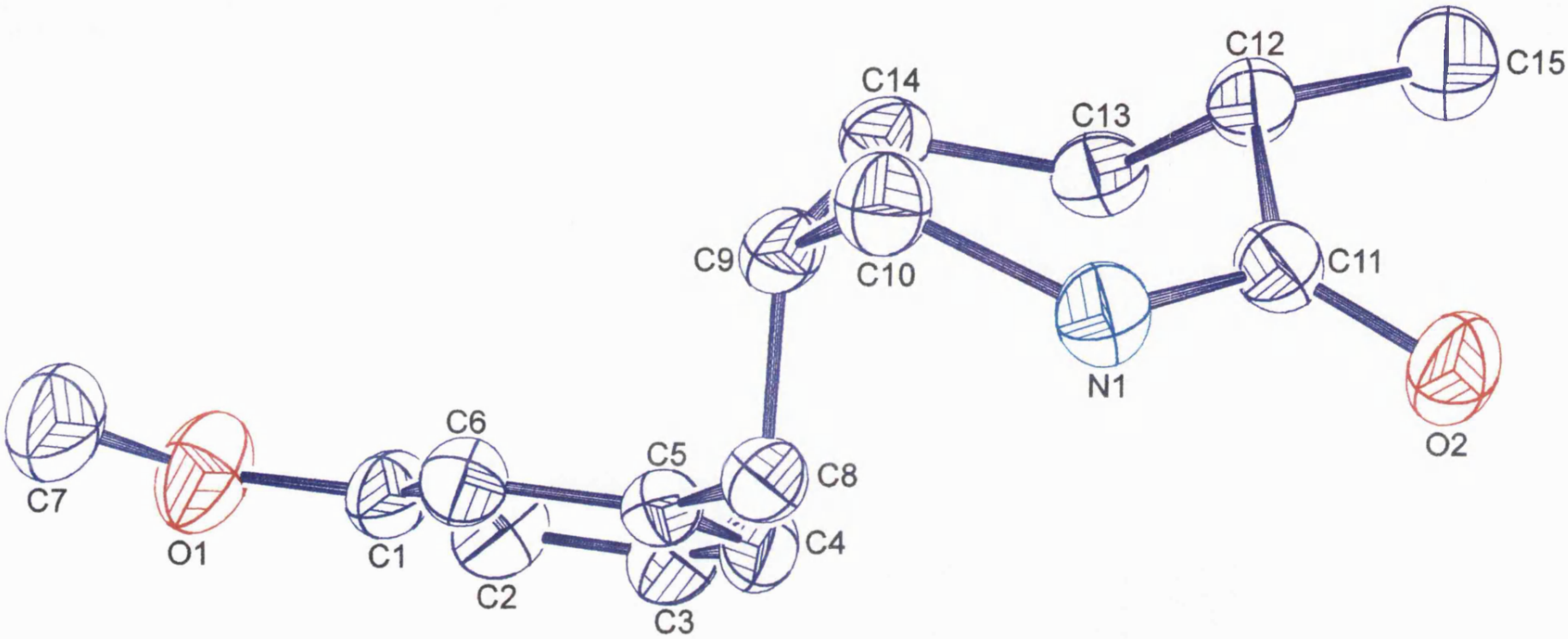
Scheme 87

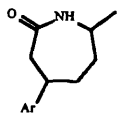
N-Methylation of (87) proved to be straightforward giving (88) in near quantitative yield [scheme 88].



Compound 86

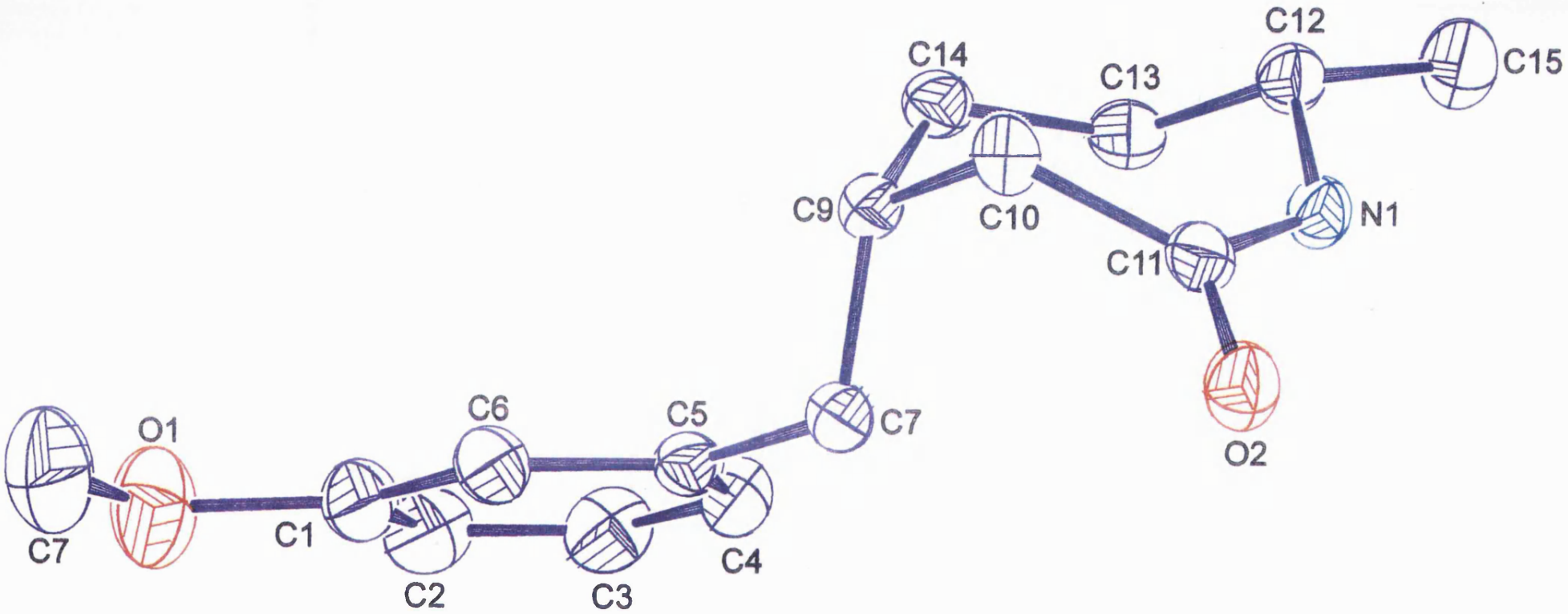
X-Ray diagram

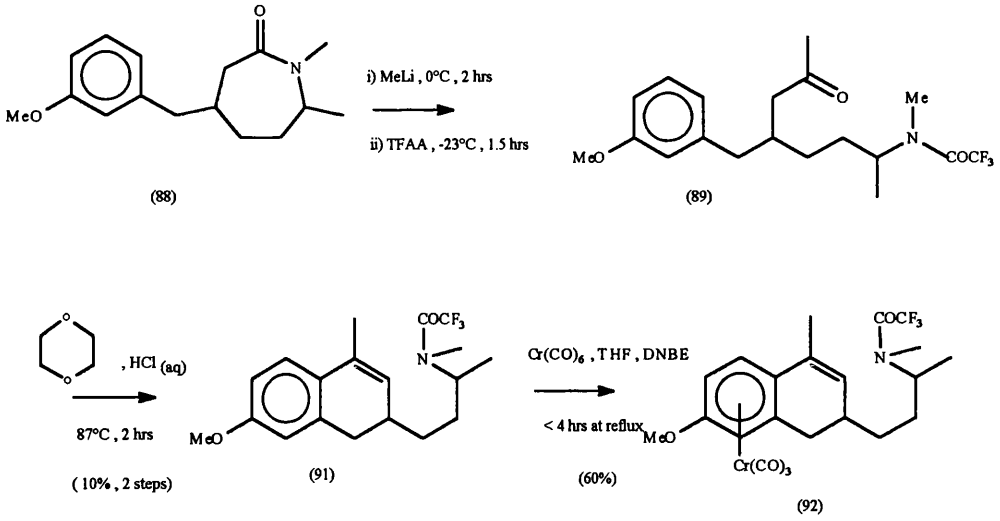

C14
C12
C15
C13
C9
C10
C11
N1
O2
C6
C5
C8
C7
O1
C1
C4
C2
C3



Compound 87

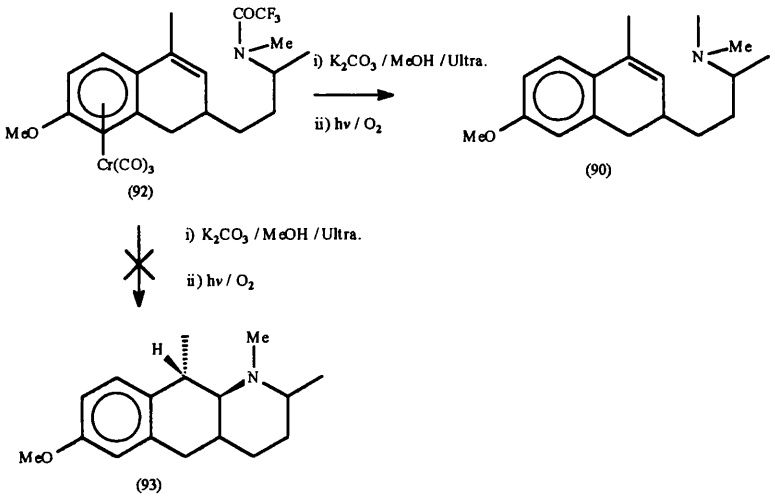
X-Ray diagram


C12
C14
C13
C15
C9
C10
N1
C11
C6
C5
C7
O1
O2
C7
C1
C2
C3
C4



Scheme 89

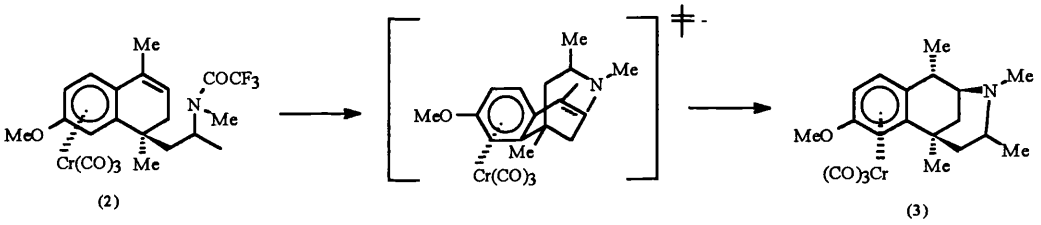
The target compound (92) was prepared by careful chromination of compound (91) using Mauffy Pauson conditions [13] (less than 4 hrs at reflux) in 60% yield. Due to the lack of chirality control in our synthesis two diastereoisomers of the azapinone (87) were isolated (a total of 4 isomers were detectable by Tlc). As the reaction conditions for cyclisation will remove the amide group and decomplexation will remove the chromium, racemic products will always be produced. It should be noted here that we did not attempt any separation of isomers for the purpose of absolute stereochemical determination of the chromium complexed intermediates and for the study of further stereochemical outcomes since attempted cyclisation of compound (92) by treatment with potassium carbonate in aqueous methanol with ultrasonication gave only (90) and failed to give any of the hoped for cyclisation product (93) [scheme 90].


COCF3
N
Me
MeO
Cr(CO)3
(92)
i) K2CO3 / MeOH / Ultra.
ii) hν / O2
N
Me
MeO
(90)
i) K2CO3 / MeOH / Ultra.
ii) hν / O2
H
Me
N
MeO
(93)

Scheme 90

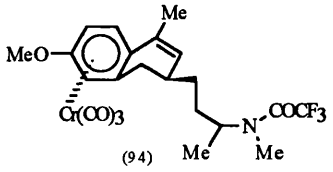
(2.7) ***Conclusion***

All of our efforts to mimic the successful cyclisation (2) - (3) noted by my predecessor Dr.Colin Williams, failed. Although we can argue that the formation of spirocycles may be less likely from a stereogenic point of view the similarity between Williams's substrate (2) and (92) is very close and the only point of difference is the location of the side chain. In Williams's compound it is probable that this occupies a pseudo axial site such that a transition state can develop optimising the chance of nucleophilic attack at the β-position of the dihydronaphthalene [scheme 91].



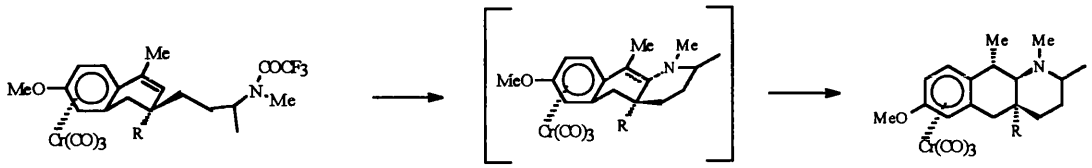
Scheme 91

In our substrate should the alkylamino substituent be held exclusively pseudo equatorial (as in (94)) [scheme 92] it is possible that its preferred conformation dictates that its amino terminus is remote from the required locus of the reaction.



Scheme 92

A way of testing this would be to replace the hydrogen atom at the allylic site (C-3) with a methyl group or preferably a larger unit R which might force a change in stereochemistry to that shown in scheme 92 where the system is set up for cyclisation [scheme 93].



Scheme 93

Chapter 3

Experimental

3.1.1 Instrumentation and experimental techniques

3.1.2 General

Glassware used for moisture sensitive reactions was heated in an oven at 120°C overnight and then allowed to cool in a dessicator over $CaCl_2$ and indicating silica. Flasks and stirrer bars were additionally flame dried under a stream of N_2 prior to use.

Solvents were evaporated with a Büchi rotary evaporator using a water aspirator or a vacuum pump as required and a water temperature of $< 40°C$ unless stated otherwise.

3.1.3 Analysis and Spectroscopy

Melting points (m.p.) were determined on commercially available apparatus (Electrochemical melting point apparatus) or Büchi 510 and are uncorrected. Elemental micro-analysis were carried out using a Carlo Ebra 1106 Elemental Analyser.

Infrared spectra were recorded in the range 4000-600cm^{-1} using a Perkin-Elmer 1600 FT-IR spectrophotometer and peaks are reported (ν_{max}) in wavenumbers (cm^{-1}) and the abbreviations br(broadened), s(strong), vs(very strong) were used to describe the peak. Samples were prepared as liquid films, nujol mulls or indicated

Proton magnetic resonance spectra were recorded on either a Joel GX FT-270 (270MHz) a Joel GX FT-400 (400MHz) or a Varian EM-360 (60MHz) spectrometer. Carbon-13 magnetic resonance spectra were recorded at 67.8MHz using 90 and 135 DEPT pulse sequences to aid in multiplicity determination. Chemical shifts (δ) are expressed in parts per million (ppm) downfield from the internal standard tetramethylsilane (TMS). The multiplicities of the resonances are denoted by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), s (sextet) and m (multiplet). The abbreviation br (broadened) is used to indicate significant broadening, whether due to rapid exchange, unresolved fine coupling or paramagnetic interference from chromium species present. Homonuclear decoupling experiments, 2D homonuclear shift correlated (COSY) and nuclear Overhauser enhancement (NOESY) spectra were used to confirm proton assignment when required.

Mass spectra were recorded using either a VG Analytical 7070E instrument with a VG2000 data system. Electron ionisation (E.I.) spectra were produced using an ionising potential of 70eV or lower (as stated). Chemical ionisation (C.I.) spectra were employed using a variety of reagent gases that are indicated in each case.

3.1.4 Solvents and Reagents

All solvents were dried and distilled before use. Petrol refers to petroleum ether with boiling point in the range 60-80°C. Tetrahydrofuran, toluene and diethyl ether were pre-dried over sodium wire and then refluxed over sodium benzophenone ketyl under a N_2 atmosphere until anhydrous. They were immediately redistilled prior to use.

3.1.5 Chromatography

Thin layer chromatography (TLC) was used extensively as a qualitative guide during reactions and for assigning the purity of compounds. *Waterman* Al SIL G/UV plates containing fluorescent indicator were used for this purpose. Visualisation of compounds was achieved by illumination under short

wavelength (254nm) ultraviolet light (when possible). Plates were developed with a variety of dips made up to recipes that are common to many standard text books (**Vogel**). These are known as potassium permanganate, phosphomolybdic acid (7% w/v) in methanol, ninhydrin (0.3% w/v) in butanol and anisaldehyde (3% w/v) in ethanol. Full development usually required heating the plates.

Medium pressure flash column chromatography was routinely employed using Amicon Matrix silica gel. Columns were packed as a slurry in the eluant and the material to be purified introduced directly as a solution in the eluting solvent or pre-absorbed onto silica gel and then applied as a thin layer to the top of the column. The eluting solvent was employed as a gradient and the pressure was developed using small hand bellows.

The experimental data presented here will be found in strict numerical order of compounds as they are numbered in the text. This, I believe, will assist in the location of data as I have myself found many a thesis where it has always appeared to me that chronological order makes data retrieval difficult and time consuming.

(3.2) *Experimental*

η^6Chromium tricarbonyl-2-[2-(cyclohexen-1-yl)]-N-methyl-N-tri fluoroacetamido aniline (23):

A suspension of the N-methyl amide (36) (170 mg, 6.4 x 10^{-4} mol) chromium hexacarbonyl (155 mg, 7.03 x 10^{-4} mol) in degassed THF (2 ml) and DNBE (18 ml) was held at reflux for 18 hrs after which time the colour had changed to deep green. The reaction mixture was filtered through celite and the solvent removed *in vacuo* to leave a yellow solid that was adsorbed onto silica and purified by flash chromatography eluting with 4:1 Hex:EtOAc to yield the title compound (23) (128mg, 45%) as an unstable yellow, oil; ν_{max} (Nujol) cm^{-1} 2905, 1940, 1870 (CO), 1670 (CO); δ_h (270MHz, $CDCl_3$) 1.50-1.95 (4H, m), 2.00-2.50 (4H, m), 3.3 (3H, d, J = 14.4 Hz, rotamers), 4.2 (1H, d, J = 14 Hz, benzylic), 4.8 (1H, d, J = 14 Hz, benzylic), 5.1-5.8 (4H, m, aromatics), 6.0 (1H, s, alkene); m/z (+) FAB in NBA,433 (M^+, 10%), 405 (5), 377 (15), 349 (base).

2-(2-Bromophenyl)-1,3-dioxole (24)

2-Bromobenzaldehyde (46 ml, 0.25 mol) which was dissolved in toluene (300 ml) containing ethylene glycol (31 g, 0.5 mol) and *p*-toluenesufonic acid (a few crystals) was heated at refluxe under Dean-Stark conditions until no more water was seen to be produced in the distillate. The toluene was removed *in vacuo* and the residue was dissolved in EtOAc (500 ml), and washed with water (300 ml) and saturated sodium bicarbonate solution (200ml). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave an oil. This was purified by distillation (86°C, 0.1 mmHg) to give the title compound as a colourless oil (48 g, 85%); ν_{max} (neat) cm^{-1} 3060, 2960, 2900, 1560 ; δ_h (60MHz, $CDCl_3$) 4.0-4.2 (4H, m, acetal), 6.1 (1H, s, benzylic), 7.25-7.75 (4H, m, aromatics); m/z (C.I. Iso-butene) 229/231 (M^+, base), 185/186 (30%), 149 (20), 119, 73.

2-[2-(1-Hydroxycyclohexanyl)phenyl]-1,3-dioxole (25)

To the bromo-compound (24) (33.3 g, 0.145 mol) in dry THF (500 ml) under a nitrogen atmosphere at -78°C was added n-butyllithium (75 ml, 0.187 mol; 2.5M in hexanes) and the mixture was stirred for 2 hrs at -78°C. Cyclohexanone (16.3 ml, 0.157 mol) in THF (50 ml) was added slowly and the resulting solution was stirred at -78°C for a further 2 hrs before being allowed to warm to R.T. overnight.

The solvent was removed *in vacuo* to leave a yellow solid which was dissolved in EtOAc (50ml) and saturated ammonium chloride solution (50ml) was added. The organic layer was separated and washed with sodium bicarbonate solution (50ml), brine (2 x 25ml) and dried ($MgSO_4$). Finally the solvent was removed *in vacuo* to leave a white oily solid. The solid was crystallised from hexane to give the title compound (25) (22.8 g, 64%); ν_{max} (nujol mull) cm^{-1} 3450 (OH), 2900; δ_h (270MHz, $CDCl_3$) 1.0-2.4 (10H, m, cyclohexane), 2.8-3.2 (1H, brs, OH), 3.5-4.1 (4H, m, ketal), 6.2 (1H, s, benzyl), 7..20-7.77 (4H, m, aromatics); m/z (low E.I.) 248 (M^+, base), 230 (M-H_2O, 60%), 50 (50), m/z (70 e.v.), 248 (M^+, 45%), 230 (M^+-H_2O, 30), 205 (base), 187, 117.

2-[2-(Cyclohexen-1-yl)phenyl]-1,3-dioxole (26)

Thionyl chloride (117 µl, 1.6 mmol) was added dropwise to a solution of (25) (200 mg, 0.8 mmol) in pyridine (5 ml) at 0°C. After 2 hrs water (10 ml), 1N sulfuric acid (2 ml) and EtOAc (20 ml) were added. The organic layer was separated and washed with sodium bicarbonate solution (2 x 10ml), brine (2 x 20ml) and then dried ($MgSO_4$) before the solvent was removed *in vacuo* to leave a brown oil. This was purified by flash chromatography eluting with 10:1 Hex:EtOAc to give the title compound (26) (110 mg, 60%) as a clear oil; δ_h (270MHz, $CDCl_3$), 1.6-1.8 (4H, m), 2.15 (2H, m, α-alkene), 2.25 (2H, m, α-alkene), 3.95-4.10 (4H, m, ketal), 5.7 (1H, m, alkene), 5.9 (1H, s, benzylic), 7.1 (1H, m), 7.25-7.40 (2H, m), 7.6 (1H,m).

2-Spiro[cyclohexane]-1,3-dihydro-1-methyoxybenzo[b]furan(28)

A solution of (25) (1.0 g, 4 mmol) in methanol (30 ml), water (5 ml) and 1 drop of 1M sulfuric acid was stirred at R.T. for 10 minutes. The methanol was removed *in vacuo* to leave a light yellow oil. This was purified by flash chromatography eluting with 9:1 Hex:EtOAc to give the title compound (28) (810 mg, 93%) as a clear oil; ν_{max} (neat) 3010, 2900, 1720 (w); δ_h (270MHz, $CDCl_3$), 1.5-1.8 (10H, m), 3.4 (3H, s, methyl), 5.95 (1H, s, benzylic), 7.1-7.3 (4H, m); δ_c (68.7MHz, $CDCl_3$), 22.4, 22.7, 25.2, 37.5, 38.9 (t, cyclohexane), 54.1 (q, methyl), 77.0 (quaternary, cyclohexane), 105.5 (d, benzylic), 120.6, 122.9, 127.6, 129.0 (d, aromatics), 137.4 (quaternary, aromatic C-3), 148.0 (quaternary, aromatic C-2); m/z 218 (M^+, 55%), 187 (M^+-MeOH, 20), 175 (base), 162.

2-Spiro[cyclohexane]-1,3-dihydro-1-ethoxy benzo[b]furan (29)

A heterogeneous mixture of EtOAc (20ml) and 1M sulfuric acid (2ml) containing (25) (700 mg, 2.8 mmol) was stirred vigorously for 16 hrs at R.T. [The layers were separated and the organic phase washed with saturated sodium bicarbonate solution, brine and dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave a yellow oil]. This was purified by flash chromatography eluting with 2-5% EtOAc/Hex to leave the title compound (29) (450 mg, 70%) as a yellow oil; ν_{max} (neat) 3010, 2890; δ_h (270MHz, $CDCl_3$), 1.25 (3H, t, J= 7 Hz, CH_3), 1.6-2.0 (10H, m), 3.7 and 3.9 (2H, m, ketal), 6.2 (1H, s, benzylic), 7.15-7.4 (4H, m); δ_c (68.7MHz, $CDCl_3$), 15.5 (q, CH_3), 22.4 (t,gamma-ether), 22.7, 25.3 (t, β-ether), 38.9, 37.5 (t, α-ether), 62.6 (t, $\underline{CH_3}CH_3$), 86.7 (quaternary, cyclohexane), 104.5 (d, hemi-acetal), 120.7, 123.0, 128.8, 129.0 (d, aromatics), 137.8 (quaternary, aromatic C-2), 148.0 (quaternary, aromatic C-1); m/z 232 (M^+, 20%), 189 (35), 117 (15).

Di-{2-spiro[cyclohexane]-1,3-dihydrobenzo [b]furan-1-yl}ether (30):

Boron trifluoride etherate (200µl, 1.6 mmol) was added to a solution of the acetal-alcohol (25) 350mg,1.4mmol) in diethyl ether (10 ml) and stirred for 1 hr. The resulting yellow solution was hydrolysed by the addition of 1M sulfuric acid (0.5 ml) and water (10 ml). The solvent was removed *in vacuo* and the residue was dissolved in EtOAc (30ml) and saturated sodium bicarbonate solution

(20ml). The organic phase was washed with brine (20ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave a clear gum. The product was isolated by flash chromatography eluting with 2% EtOAc:Hex to give (30A) and (30B) as colourless crystalline solids; I.R., M.S., ^{1}H NMR, MA, were identical for both isomers [Found: (30A) C, 80.3; H, 7.82; (30B), C, 79.8%; H, 7.78; $C_{26}H_{30}O_3$ requires: C, 79.96; H, 7.74%]. M.p. (8A) 137.5-138°C (Hex), (30B), 127-129°C (Hex); ν_{max} (Nujol) cm^{-1} 2850, 1435, 1370. δ_h (270MHz, $CDCl_3$) 1.3-1.90 (20H, m, cyclohexane), 6.45 (2H, s, hemiacetal), 6.90-7.20 (8H, m); δ_c (68.7MHz, $CDCl_3$), 22.5,22.9 (t, β-ether), 25.4 (t, gamma-ether), 37.8, 39.3 (t, α-ether), 87.4 (quaternary, cyclohexane), 101.5 (d, hemi-acetal), 120.6, 123.0, 127.7, 128.8 (d, 4 x aromatics), 138.2 (quaternary, C-2 aromatic), 148.2 (quaternary, C-1 aromatic); m/z 390 (M^+, 3%), 260, 232 (55), 189 (base); C.I. (iso-butane) 390 (M^+, 5%), 229 (5), 203 (10), 187 (base, ether cleavage); [(30A) Found:390.2170, (30B) Found: 390.2164 $C_{26}H_{30}O_3$ requires: 390.2195, errors of 8 and 6 ppm respectively].

2-[2-(Cyclohexen-1-yl)]-benzonitrile (33)

The experimental procedure in the literature [98]was followed exactly except that the reaction time in pyridine was reduced to 1 hr and at reflux. Work up gave, from (33) (12.1 g, 44.3 mmol), 7.9 g of crude material and 6.0g, after chromatography (75%).

2-(1-Cyclohexenyl) benzylamine (34)

A solution of the nitrile (33) (2 g, 11 mmol) in THF (40 ml) was added dropwise to a suspension of LAH (440 mg, 12.1 mmol) in THF (100 ml) at 0°C. The mixture was heated to reflux whereupon the colour of the reaction changed from orange to golden brown. After 1 hr the reaction mixture was cooled and saturated sodium potassium tartrate solution was added until all the excess LAH was decomposed. The suspension was filtered, washed extracted with ether and the solvent was removed *in vacuo* to leave an oil. This was dissolved in EtOAc and water and washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave a clear oil. This was purified by flash chromatography eluting with EtOAc containing butylamine (1-7%) to leave the title compound (34)

(1.7 g, 82%) as a clear oil; ν_{max} (neat) cm^{-1} 3360 (NH_2), 3260, 3100, 2910, 2190, 1590; δ_h (270MHz, $CDCl_3$) 1.5 (2H, s, removed with D_2O, NH_2), 1.5-1.8 (4H, m, β-alkene), 2.05-2.20 (4H, m, α-alkene), 3.74 (2H, s, benzylic), 5.5 (1H, p, J = 1.5 Hz alkene), 7.0 (1H, m), 7.14 (2H, m), 7.25 (1H, m).

2-[2-(Cyclohexen-1-yl)]-N-trifluoroacetamido aniline(35):

Trifluoroacetic anhydride (1.4 ml, 9.9 mmol) was added to a solution of the amine (34) (1.7 g, 9 mmol) and pyridine (800 µl, 9.9 mmol) in DCM (50 ml) and stirred for 12 hrs at R.T. The reaction mixture was dissolved in EtOAc, then washed with *iced* saturated sodium bicarbonate solution and brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave an oil which was purified by flash chromatography (6:1 Hex:EtOAc) and crystallised from hexane to leave the title compound (35) (2.0 g, 77%) as a white solid (hexane); M.p. 106-107°C. [Found; C, 63.7; H, 5.73; N, 4.92%; $C_{15}H_{16}NOF_3$ requires: C, 63.58; H, 5.70; N, 4.94%]; ν_{max} (Nujol) cm^{-1} 3220 (amine), 2960, 1700 (carbonyl); δ_h (270MHz, $CDCl_3$). 1.6-1.8 (4H, m, β-alkene), 2.10-2.25 (4H, m, α-alkene), 4.55 (2H, d, J = 6 Hz, benzylic), 5.60 (1H, p, J = 1.5 Hz, alkene), 4.55 (2H, d, J = 6 Hz, benzylic), 5.60 (1H, p, J = 1.5 Hz, alkene), 6.56 (1H, brs, amide), 7.1-7.4 (4H, m); m/z 283 (M^+, 12%), 228 (10), 170 (base), 157 (90), 142 (90), 128 (35).

2-[2-(Cyclohex-en-1-yl)]-N-methyl-N-trifluoroacetamido aniline (36):

To the solid amide (35) (1.2 g, 3.95 mmol) and sodium hydride (65% dispersion in mineral oil) (131 mg, 4.35 mmol) was added THF (50 ml) and the mixture was stirred for 10 minutes at R.T. Methyl iodide (492 µl, 7.9 mmol) was added and the reaction was stirred for a further 10 minutes. The reaction mixture was then poured onto ice and extracted with DCM. The combined extracts were washed with *iced* brine, dried ($MgSO_4$), filtered and the solvents removed *in vacuo*. The residue was purified by flash chromatography eluting with 8:1 Hex:EtOAc to give the title compound (36) (1.22 g, quantitative yield); [Found; C, 63.30; H, 5.66; N, 5.82%; $C_{16}H_{18}NOF_3$ requires: C, 63.59; H, 5.70; N,

5.94%]; [m/z requires: 297.13405; Found: 297.13505 error of 3 ppm]; ν_{max} (neat) cm^{-1} 3360 (carbonyl overtone), 3050, 2920, 1680 (amide); δ_h (270MHz, $CDCl_3$), 1.50-1.80 (4H, m, β-alkene), 2.00-2.15 (4H, m, α-alkene), 2.90 (3H, d, J = 14 Hz, methyl rotamer), 4.60 (2H, d, J = 16 Hz, benzylic rotamer), 5.50 (1H, s, alkene), 7.0-7.3 (4H, m); [Heating the sample to 100°C in DMSO gives δ_h: 2.9 (3H, s) and 4.60 (2H, s)]; δ_C (68.7MHz, $CDCl_3$), 22.5, 23.1 (t, β-alkene), 27.6 (t, α-CH alkene), 31.6 (t, α-alkene), 33.2 / 34.0 (q, N-Methyl, rotamers), 50.1 / 51.0 (t, α-amide, rotamers), 126.5 (d, alkene), 127.4, 128.1, 128.6, 129.3 (d, 4 x aromatics), 132.4 (quaternary, C-alkene), 137.2 (quaternary, C-CH_2), 146.2 (quaternary, alkene), 157.2 (m, CF_3); m/z 297 (M^+, 5%), 228 (5), 170 (base), 157, 155, 142 (80).

η^6-(Chromium tricarbonyl)-2-[2-(cyclohe-en-1-yl)]-N-methyl aniline(37):

The N-trifluoroacetamide (23) was treated with a variety of basic aqueous conditions in solvents under a variety of conditions to produce each time the same compound which could be isolated by flash chromatography eluting with EtOAc containing butylamine (1-3%) to leave the title compound (37) as a yellow oil; ν_{max} (neat) cm^{-1}, 3350 (amine), 2935, 2854, 1957, 1878, 1445; δ_h (270MHz, $CDCl_3$) 1.60-1.80 (4H, m), 2.10-2.20 (4H, m), 2.55 (3H, s, methyl), 3.43 (1H, J = 14 Hz, benzylic), 3.62 (1H, J = 14 Hz, benzylic), 5.15 (1H, t, J = 6 Hz, aromatic), 5.35-5.55 (3H, m, aromatics), 5.9 (1H, m, alkene); δ_C (68.7MHz, $CDCl_3$), 21.6, 22.9 (t, β-alkene), 25.5 (t, α-CH-alkene), 31.4 (t, α-alkene), 36.6 (q, N-methyl), 52.0 (t, benzylic), 88.7, 89.7, 94.9, 96.7 (d, aromatics), 111.6 (quaternary, C-alkene), 116.3 (quaternary, C-alkyl), 131.1 (d, alkene), 132.6 (quaternary, alkene).

2-[2-(Cyclohexen-1-yl)]-N-methyl aniline(39):

A solution of the chromium complex (37) in diethyl ether (30ml) was allowed to stand in direct sunlight with only a cotton wool bung as protection. The solution was shaken every hour until after approximately 3 hrs a green percipitate had settled out leaving a clear solution. This was filtered through celite and the solvent removed *in vacuo* to leave an oil, which was purified by flash chromatography eluting with EtOAc containing butylamine (1-3%) to leave the title compound (39) as a pale yellow oil; ν_{max} (neat) cm^{-1} 3320 (amine), 3021, 2927, 2835, 1475, 1445; δ_h (270MHz,

$CDCl_3$). 1.60-1.90 (4H, m), 1.70 (1H, brs, NH), 2.20-2.36 (4H, m), 2.45 (3H, s, methyl), 3.8 (2H, s, benzylic), 5.65 (1H, s, alkene), 7.1-7.5 (4H, aromatics). Conversion of this product to 2-[2-(cyclohexen-1-yl)-N-Methyl-N-trifluoroacetamido aniline (36) by reaction with trifluoroacetic anhydride and pyridine in DCM proved the assignment of structure was correct.

2-Hydroxy-2-(2-propenyl)-1,2,3,4-tetrahydronaphthalene (42):

A suspension of manganese (44 g, 788 mmol) and iodine (1.43 g, 113 mmol) in THF (600 ml) was refluxed for 2 hrs and then cooled to R.T. Allyl bromide (59 ml, 675 mmol) in THF (50ml) and β-tetralone (30 ml, 225 mmol) in THF (50ml) were added, and the resulting mixture was refluxed for 14 hrs.

The reaction was cooled and the solvent removed *in vacuo* to leave a dark oil which was dissolved in ether and brine. The aqueous layer was separated and extracted a further three times with ether (3 x 30ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the solvents removed *in vacuo* to leave a red oil. This was purified by flash chromatography eluting with 5% EtOAc:cyclhex to give the title compound (42) (25.5g, 60%)as a clear oil. b.p. 122-4°C; ν_{max} (neat) cm^{-1} 3401 (OH), 3074, 3018, 2925, 1495, 1452; δ_h (250MHz, $CDCl_3$) 1.7 (1H, s, OH), 1.75-1.95 (2H, m, C-3), 2.35 (2H, d, J = 7 Hz, α-alkene), 2.85 (2H, d, J = 11 Hz, benzylic), 2.90-3.10 (2H, m), 5.10-5.25 (2H, m, alkene), 5.95 (1H, ddt, J = 18, 11, 7 Hz, alkene), 7.0-7.2 (4H, m); δ_c (68.7Mhz,$CDCl_3$), 26.0 (t, benzylic), 33.6 (t, benzylic-α-ether), 41.6 (t, α-ether), 45.5 (t, α-alkene), 70.3 (quaternary, ether), 119.0 (t, alkene), 125.7, 125.8, 128.6, 129.5 (d, 4 x aromatics), 133.3 (d, alkene), 134.3, 135.4 (quaternary, aromatics); m/z 188 (M^+, 5%), 170 (M^+-H_2O, 5%), 147 (M^+-allyl, base), 129 (70), 117 (45), 104.

2-(3-Hydroxypropyl)-2-hydroxy-1,2,3,4-tetrahydronaphthalene (43):

Borane tetrahydrofuran complex (5.9 ml, 5.9 mmol) was added to a solution of the alkene (42) (1 g, 5.3 mmol) in THF (15 ml) at 0°C. After 14 hrs sodium hydroxide (2M, 22.6 ml, 45 mmol) was added and the resulting mixture was. Hydrogen peroxide (2.56 ml, 45 mmol) was then added cautiously and the solution was heated at reflux for a further hour before being cooled and extracted with EtOAc.

The combined organic extracts were washed with sodium *meta*-bisulfite until a negative peroxide test was given, then dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography eluting with 70% EtOAc:Cyclhex to yield the title compound (43) (910 mg, 84%) as a clear oil; ν_{max} (neat) cm^{-1}, 3343 (broad), 3061, 2931, 1453, 1059; δ_h (250MHz, $CDCl_3$), 1.65-1.95 (6H, m, C-3, α,β-alcohol), 2.60 (2H, s, 2 x OH), 2.75-3.00 (2H, m, benzylic), 2.85 (2H, s, benzylic), 3.70 (2H, t, J = 6 Hz, CH_2OH), 7.0-7.14 (4H, m, aromatics); m/z (Thermal spray) 224 (MNH_4^+, 65%), 207 (MH^+, 35), 189 ($M-H_2O$, 50), 180 (65).

2-(Tertiarybutyldimethylsilyloxy)-2-(2-propenyl)-1,2,3,4-tetrahydronaphthalene (46)[107]:

To a stirred solution of the alcohol (42) (1.93 g, 10.3 mmol) and 2,6-lutidine (1.8 ml, 15.4 mmol) in DCM (15 ml) was added dropwise a solution of TBDMS-triflate (5.92 ml, 25.8 mmol) in DCM (15 ml) at 0°C. After addition the cooling bath was removed and the reaction was allowed to stir for 40 minutes at R.T. The reaction mixture was diluted with ether (150 ml) and water (50 ml). The layers were separated and the organic phase washed with brine before being dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave a brown oil. This was purified by a short filtration column (SiO_2:cyclohexane) to give the title compound (46) (3.2 g, quant) as a clear oil. B.p. 65°C; ν_{max} ($CHCl_3$) cm^{-1} 3050, 2956, 1495, 1250, 1078, 1045; δ_h (250MHz, $CDCl_3$) -0.2 (3H, s, Me), 0.20 (3H, s, Me), 0.90 (9H, s, ^tBu), 1.85-2.00 (2H, m, C-3), 2.4 (2H, d, J = 7 Hz, α-alkene), 2.80 (1H, dt, J = 16, 6 Hz, C-4), 2.90 (2H, d, J = 8 Hz, benzylic), 3.05 (1H, dt, J = 16, 7 Hz, C-4), 5.1-5.2 (2H, m, alkene), 6.05 (1H, ddt, J = 18, 11, 7 Hz, alkene), 7.05-7.2 (4H, m); δ_c (100.4MHz, $CDCl_3$), -2.4 (q, methyl), -2.0 (q, methyl), 18.3 (s, ^tbu), 26.8 (t, benzylic), 34.5 (t, benzylic-C-O), 42.4 (t, CH_2-benzylic), 45.8 (t, CH_2-alkene), 73.8 (s, C-O), 117.4 (t, alkene), 125.2, 125.6, 128.5, 129.4 (d, 4 x aromatics), 134.6 (d, alkene), 135.3, 135.8 (s, 2 x aromatics); m/z 260 (M^+-allyl, 25%), 245 (M^+-^tBu, 50), 203, 169, 147; [Found; C, 75.43; H, 10.00%; $C_{19}H_{30}OSi$ requires: C, 75.1; H, 10.1%].

2-(3-Hydroxypropyl)-2-(tertiarybutyldimethylsilyloxy)-1,2,3,4-tetrahydronaphthalene (47)[102]:

Borane tetrahydrofuran complex (59.5 ml, 59.5 mmol) was added dropwise to a stirred solution of the alkene (46) (18 g, 59.5 mmol) in THF (200 ml) at 0°C. After 1 hr sodium hydroxide solution (1N, 300ml, 600mmol) followed by hydrogen peroxide (34ml, 600mmol), was added cautiously. After a further 2 hrs, water (200ml) was added and the organic products were extracted with EtOAc (3 x 150ml). The combined organic extracts were washed with sodium metabisulphite until a negative peroxide test was obtained. They were then dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave a clear oil which required no further purification giving the title compound (47) (25.5 g, 60%). B.p. 122-4°C; ν_{max} (neat) cm^{-1} 3401 (OH), 3074, 3018, 2925, 1495, 1452; δ_h (250MHz, $CDCl_3$) 1.7 (1H, s, OH), 1.75-1.95 (2H, m, C-3) 2.35 (2H, d, J = 7 Hz, α-alkene), 2.85 (2H, d, J = 11 Hz, benzylic), 2.90-3.10 (2H, m), 5.10-5.25 (2H, m, alkene), 5.95 (1H, ddt, J = 18, 11, 7 Hz, alkene), 7.0-7.2 *(4H,* m); δ_c (68.7MHz, $CDCl_3$), 26.0 (t, benzylic), 33.6 (t, benzylic-α-ether), 41.6 (t, α-ether), 45.5 (t, α-alkene), 70.3 (quaternary, ether), 119.0 (t, C-OH), 42.8 (t, CH_2-benzylic), 63.4 (t, α-OH), 73.9 (quaternary), 125.5, 125.7, 128.5, 129.3 (d, aromatics), 135.3, 135.6 (quaternary, aromatics); m/z (C.I.) 321 (MH^+, 25%), 206 (base), 171; [Found; C, 71.30; H, 10.09%; $C_{19}H_{32}O_2$ requires: C, 71.20; H, 10.06%].

2-(3-N-Phthalimidopropylamino)-2-(tertiarybutyldimethylsilyloxy)-1,2,3,4-tetrahydronaphthalene (48)[108]:

To a solution of the alcohol (47) (10 g, 31 mmol), triphenylphosphine (9.8 g, 37mmol) and phthalide (5 g, 37 mmol) in THF (200 ml) at 0°C was added diethylazodicarboxylate (5.9 ml, 37 mmol) slowly. The reaction mixture was allowed to warm to R.T. overnight before the solvent was removed *in vacuo* and the residue was adsorbed onto silica and purified by chromatography eluting with 10% EtOAc:cyclhex to give the title compound (48) (12.4 g, 89%) as a clear oil. B.p. 250-255°C; ν_{max} ($CHCl_3$)cm^{-1} 3692 (overtone), 2930, 1772, 1713 (vs, carbonyl) 1240; δ_h (250MHz, $CDCl_3$) 0.20 (3H, s), 0.20 (3H, s), 0.90 (9H, s, ^tBu), 1.65-2.05 (6H, m), 2.80 (1H, dt, J = 18, 6 Hz, C-3), 2.90 (2H, s,

benzylic), 3.05 (1H, dt, J = 18.0, 7.0 Hz), 3.80 (2H, t, J = 7.0 Hz, CH_2-NPth, 7.05-7.2 (4H, m), 7.8 (2H, dd, J = 6.0, 3,0 Hz, γ-carbonyl), 7.95 (2H, dd, J = 6.0, 3.0 Hz, β-carbonyl); m/z (TSP) 467 (MNH_4^+), 450 (MH^+), 335 (MNH^+_4-OTBDMS), 318 (MH^+-OTBDMS).

2-(Hydroxy)-2-(3-N-phthalimidopropylamino)-1,2,3,4-tetrahydronaphthalene (48a):

A solution of the protected alcohol (48) (1g, 2.9 mmol) in 5 M HCl and THF (25ml, 4:1) was heated at refluxed overnight under an Argon atmosphere. The reaction mixture was cooled to R.T. and the solvent was removed *in vacuo* and then 2 M NaOH was added until pH >9. The product were extracted with ether (3 x 50ml), combined, washed with brine (50ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to leave a pale yellow oil (2.5g). Chromatography 5-35% EtOAc/Cyclhex gave starting material (48) (600mg, 30%) and the title compound (48a) (701mg, 40%) as a white solid. M.p. 92-93°C. Rf .0.33 (40% EtOAc/Cyclhex) and a mixture of the 1- and 2- alkenes (49) and (49a) (388mg,27%); ν_{max} ($CHCH_3$) cm^{-1}, 3597 (w), 3029 (w), 3011 (w), 2935 (s), 1773 (w), 1713 (vs); δ_h (250 MHz, $CDCl_3$), 1.80 (6H, m), 2.75 (1H, dt, J= 14.0, 6.5 Hz, benzylic), 2.80 (2H, d, J= 6.0 Hz, benzylic), 3.00 (1H, dt, J= 14.0, 6.5 Hz, benzylic), 3.77 (2H, t, J= 6.7 Hz, CH_2-N), 7.05 (4H, m, aromatics), 7.78 (4H, m, Phthalimide); m/z C.I. (NH_3) +ve, 335 (M^+ [MNH_4^+-H_2O]), 336 (MH^+), 353 (MNH_4^+), 318 (MH^+-H_2O) +ve Thermospray , 335, 336, 358 (MNa^+), 318.

2-(3-N-Phthalimidopropylamino)-3,4-dihydronaphthalene (49)[110]:

Boron trifluoride etherate (9.22 ml, 75 mmol) was added (in one aliquot) to a solution of the silyl ether (48) (11.3 g, 25 mmol) in DCM (100 ml) at 0°C. After 72 hrs the reaction was quenched by the rapid addition of sodium bicarbonate (excess) and extracted with ether (4 x 100ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave an oil. This was purified by flash chromatography eluting with 10% EtOAc:cyclhex to give the title compound (49) (6.64 g, 85%) as a white solid. M.p. 59-60°C; ν_{max} cm^{-1} (neat) 3466 (overtone), 3015, 2928, 1772, 1713, 1397; δ_h (250MHz, $CDCl_3$), 1.8 (2H, p, J = 7.0 Hz), 2.15 (4H, 2 x t, J = 8.0, 7.0 Hz, α-alkene), 2.7 (2H, t, J = 8.0 Hz, benzylic), 3.63 (2H, t, J = 7.0 Hz, α-Pht, 6.15 (1H,s, alkene), 6.8-7.0 (4H, m), 7.6 (2H, dd, J = 6.0, 3.0 Hz, γ–

carbonyl), 7.75 (2H, dd, J = 6, 3 Hz, β-carbonyl); δ_C (67.8MHz, $CDCl_3$), 26.2 (t, CH_2), 27.2 (t, CH_2-alkene), 28.1 (t, CH_2-benzylic), 34.6 (t, benzylic), 37.8 (t, CH_2-N), 123.0 (d, alkene), 123.3, 125.6, 126.5, 126.3 (d, 4 x aromatics), 127.3 (d, 2 x *m*-phthalimide), 133.9 (s, phthalimide), 134.0 (d, o-phthalimide), 134.4, 134.7 (quaternary, 2 x aromatics), 140.4 (quaternary, alkene); m/z (Thermal spray) 335 (MNH_4^+), 318 (MH^+), 206, 132; Low E.I. 317 (M^+, base), 263 (20%), 171 (20), 30 (20); [Found; C, 79.3; H, 6.13; N, 4.50%; $C_{21}H_{19}NO_2$ requires: C, 79.46;H, 5.99; N, 4.41%]; [m/z Found; 317.1380, $C_{21}H_{19}NO_2$ requires: 317.1415, error of 3.5 ppm].

(49) and (49a) from (48):

To a solution of the alcohol (48) (100 mg, 3 x 10^{-4}mol) in dry pyridine (3ml) was added either thionyl chloride (45 µl, 6 x 10^{-4} mol) or methane sulfonyl chloride (47 µl, 6 x 10^{-4} mol) at 0°C. After a short period (~30 minutes for thionyl chloride, or overnight for methane sulfonyl chloride), the reaction was poured into 2M hydrochloric acid and extracted with ether. The combined organic extracts were dried ($MgSO_4$), filtered and the solvents removed *in vacuo*. The resulting clear oil was purified by flash chromatography eluting with 10% EtOAc:cyclhex to leave (49) and (49a) which were identical to the authentic products by ^{1}H NMR. Ratio = 2:1.

2-(3-Aminopropyl)-3,4-dihydronaphthalene (50)[111]:

Hydrazine hydrate (2.61 ml, 85 mmol) was added to a solution of compound (49) (6.64 g, 21 mmol) in ethanol (50 ml) and heated at reflux for 30 minutes. A white solid formed which was collected and added to 2M hydrochloric acid, which was then made basic with 2M sodium hydroxide and extracted with ether (3 x 50ml). The combined organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography eluting with 100:5:1 DEA to give the title compound (50) (3.4 g, 87%) as a pale yellow oil; ν_{max} (neat) cm^{-1} 3368 (NH_2), 3014, 2928, 1647, 1487; δ_h (250MHz, $CDCl_3$) 1.65 (4H, p, J = 7.0 Hz, β-NH_2 + NH_2), 2.25 (4H, t, J = 8.2 Hz, α-alkene), 2.75-2.85 (4H, 2 x t, J = 8.2, 7.0 Hz, benzylic + α-NH_2), 6.22 (1H, s, alkene), 6.95-7.15 (4H, m); m/z (Thermal spray), 188 (MH^+, base).

2-(3-N-Trifluoroacetamidopropyl)-3,4-dihydronaphthalene (51):

Trifluoroacetic anhydride (3.11 ml, 22 mmol) was added slowly to a solution of the amine (50) (3.4 g, 18.2 mmol) and pyridine (1.8 ml, 22 mmol) in DCM (50 ml) at 0°C. After 1 1/2 hrs brine was added and the organic phase was extracted with diethyl ether (3 x 30ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to leave an oil. This was purified by flash chromatography eluting with 10% EtOAc:cyclhex to yield the title compound (51) (4.8 g, 93%) as a white solid which was rystallised from hex/EtOAc. M.p. 56°C; ν_{max} (neat) cm^{-1} 3110, 2933, 1703, 1557, 1181; δ_h (250MHz, $CDCl_3$), 1.85 (2H, p, J = 7.4 Hz, β-amide), 2.25 (4H, 2 x t, J = 7.4, 8.3 Hz, α-alkene), 2.8 (2H, t, J = 8.3 Hz, benzylic), 3.4 (2H, q, J = 7.4 Hz, α-amide), 6.25 (1H, s, alkene), 6.3-6.4 (1H, brs, amide), 6.95-7.20 (4H, m); m/z (C.I.) 301 (MNH_4^+, base).

2-(3-N-Methyl-N- trifluoroacetamidopropyl)-3,4-dihydronaphthalene (52):

To a stirred suspension of sodium hydride (60% dispersion in mineral oil) (570 mg, 19 mmol) in THF (50 ml) was added a solution of the amide (51) (4.8 g, 17 mmol) in THF (50 ml) slowly at 0°C. The cooling bath was removed and methyl iodide (2.12 ml, 34 mmol) was added cautiously. After 2 hrs brine was added and the solvent was removed *in vacuo*. The remaining aqueous layer was extracted with ether, combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography eluting with 10% EtOAc:cyclhex to leave the title compound (52) (3.82 g, 78%) as a yellow oil. B.p. 194-198°c; ν_{max} (neat) cm^{-1} , 3383 (overtone), 3016, 2933, 1696; [Found; C, 64.6; H, 6.15; N, 4.60; $C_{16}H_{18}NOF_3$ requires: C, 64.64; H, 6.10; N, 4.71%]; δ_h (250MHz, $CDCl_3$), 1.85 (2H, p, J = 8 Hz, β-amide), 2.25 (4H, 2 x t, J = 8, 7 Hz, α–alkene), 2.82 (2H, t, J = 8 Hz, benzylic), 3.05 (1H, s, methyl rotamer), 3.15 (2H, q, J = 1.4 Hz, methyl rotamer), 3.45 (2H, q, J = 8 Hz, α-amide), 6.25 (1H, s, alkene), 6.95-7.2 (4H, m); δ_C (67.8MHz, $CDCl_3$), 27.2, 28.1, 28.1 (t, 3 x CH_2), 34.1/ 34.3 (t, $\underline{CH_2}CH_2N$, rotamers), 34.5/ 34.9 (q, N-methyl, rotamers), 49.4 (t, CH_2-N), 122.9/ 123.2 (d, alkene, rotamers), 125.5, 125.6, 126.5, 127.2 (d, 4 x aromatics), 134.4, 134.6 (s, 2 x aromatics), 140.3/139.8 (s, alkene, rotamers); m/z 297 (M^+, 50%), 266 (2), 228 (20), 170 (35), 142

(base); Low E.I. 297 (M^+ base), 228 (10%), 168 (10), 142 (10), 44 (20); [Found; 297.1327, $C_{16}H_{18}NOF_3$ requires: 297.1340, error of 1.3 ppm].

η^6Chromium tricarbonyl-2-(3-N-methyl-N-trifluoroacetamidopropyl)-3,4-dihydronaphthalene (53):

A suspension of (52) (1.4 g, 4.7 mmol) and chromium hexacarbonyl (1.3 g, 5.7 mmol) in degassed di-n-butyl ether (36 ml) and THF (4 ml) was heated at reflux in the absence of light for 18 hrs. The solvents were then removed *in vacuo* and the residue adsorbed upon silica and purified by flash chromatography eluting with 10 - 20% EtOAc:cyclhex to yield first the starting material (52) as an oil (310 mg, 21%) and then the title compound (53) (1.44 g, 91%) as a red brown oil, which is light sensitive; [Found; C, 52.60; H, 4.35; N, 3.18; $C_{19}H_{18}CrNOF_3$, requires: C, 52.66; H, 4.19; N, 3.23%]; ν_{max} ($CHCl_3$) cm^{-1}, 3020 (s), 2942,
1963 (vs), 1888 (vs), 1692 (s); δ_h (250MHz, $CDCl_3$), 1.0-2.9 (8H, m), 3.05 (1H, s, methyl rotamer), 3.15 (2H, s, methyl rotamer), 3.3-3.6 (2H, m, α-amide), 5.10-5.42 (4H, m, aromatics), 5.9 (1H, brs, alkene); m/z (CI) 451 (MNH_4^+, 80%), 434 (MH^+, 5), 315 (base), 200 (90); [Found; 433.0607, $C_{19}H_{18}CrNOF_3$requires: 433.0593, error of -3.4ppm].

2-(Tertiarybutyldimethylsilyloxy)-2-(3-{O-trifluoroacetyl}hydroxypropyl)-1,2,3,4-tetrahydronaphthalene (60):

Trifluoroacetic anhydride (242 µl, 1.72 mmol) was added to a solution of the alcohol (47) (500 mg, 1.56 mmol) and pyridine (150 µl, 1.82 mmol) in DCM (10 ml) at 0°C. After 1 hr brine was added and the reaction mixture was extracted with ether. The combined organic extracts were combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The remaining oil was purified by flash chromatography eluting with 2% EtOAc: hex to leave the title compound (60) (350 mg, 76%) as a clear oil. B.p. 148-150°C. R_f. 0.52 (5% EtOAC/ hexane); ν_{max} (neat) cm^{-1}, 3357 (w, carbonyl overtone), 3019 (w), 2933 (s), 2857 (s), 1737 (s, Carbonyl), 1357 (s); δ_h (270MHz, $CDCl_3$) -0.10 (3H, s, Me), 0.10 (3H, s, Me), 0.90 (9H, s, ^tBu), 1.66 (2H, dd, J = 7, 10 Hz, CH_2-benzylic), 1.88 (2H, p, J =

6.5 Hz, β-ester), 1.98 (2H, t, J = 6.5 Hz, γ-ester), 2.8 (1H, dt, J = 18.1, 6.5 Hz, benzylic), 2.93 (2H, d, J = 6.0 Hz, benzylic), 3.4 (1H, dt, J = 18.0, 6.5 Hz, benzylic), 4.40 (2H, t, J = 6.5 Hz, α–ester), 7.05-7.2 (4H, m); δ_C (67.8MHz, $CDCl_3$), -2.0, -2.3 (q, Me), 18.3 (quaternary, ^tBu), 25.8 (q, ^tBu), 27.0 (t, C-4), 27.1 (t, C1'), 34.4 (t, C1), 37.4 (t, C3), 42.8 (t, β-ester), 70.5 (t, CH_2-O), 73.4 (quaternary, C-O), 125.7, 125.9, 128.6, 129.3 (d, 4 x aromatics), 135.0, 125.4 (s, 2 x aromatics), 172.0 (quaternary, carbonyl) m/z E.I. (70eV), 341 (M^+-[$Si(Me)_2{}^tBu$], 2%), 299 (8%), 263 (25%), 221 (65%), 171 (90%), 153 (62%), 129 (78%), 75 (100%); m/z C.I. (iso-butane), 341 (4%), 303 (20%), 267 (22%), 171 (100%).

2-(3-{O-Trifluoroacetyl}hydroxypropyl)-3,4-dihydronaphthalene (61):

The same procedure that was used for the preparation of (49) from (48) was repeated here. Compound (60) (490 mg, 1.18 mmol) gave, after flash chromatography (5% EtOAc:cyclhex) the title compound (61) (250 mg, 75%); ν_{max} (neat) cm^{-1} 3016, 2929, 1784; δ_h (270MHz, $CDCl_3$) 2.0 (2H, p, J = 8 Hz, β-ester), 2.25 (4H, p, J = 8 Hz, β-alkene), 2.80 (2H, t, J = 8 Hz, benzylic), 4.4 (2H, t, J = 7 Hz, α-ester), 6.25 (1H,s, alkene), 6.95-7.20 (4H, m); m/z 284 (M^+, 50%), 170 (20), 153 (60), 129 (M-$(CH_2)_3OCOCF_3$, Base).

η^6-Chromium tricarbonyl-2-(3-{O-trifluroacetyl}hydroxypropyl) -3,4-dihydronaphthalene (62):

A solution of the protected alcohol (61) (300 mg, 1.06 mmol) chromium hexacarbonyl (265 mg, 1.2 mmol), THF (4 ml) and DNBE (36 ml) was heated at reflux in the absence of light for 18 hrs. The solvent was removed *in vacuo* and the residue was adsorbed onto silica and purified by flash chromatograhy (20% EtOAc: hex) to give starting material (50 mg) and a mixture of (33) (99), (62) and (98) (300mg). Compound (62) is very unstable under normal conditions and no data were obtained other than the ^1H NMR spectrum which was complex and showed both complexed and non-complexed product. Proof of the structure of (62) was obtained by releasing the free alcohol through de-chromination and comparison of the alcohol with a sample made previously. δ_h (270MHz, $CDCl_3$) 4.55 (5H, t, J = 7 Hz, α-ester), 5.25-5.6 (5H, m, aromatics), 6.05 (1H, s, alkene-complexed), 6.40 (1H, s, alkene-uncomplexed), 7.05-7.2 (5H, m, aromatics uncomplexed).

2-(3-Phenylacetylpropyl)-2-(tertiarybutyldimethylsliyloxy)-1,2,3,4-tetrahydronaphthalene (63):

Benzoyl chloride (435µl, 3.75mmol) was added rapidly to a stirring solution of the alcohol (47) (1g, 3.1mmol) pyridine (303µl, 3.75mmol) in DCM (4ml). A white precipitate was formed quickly and after 2 hrs no starting material was seen by Tlc analysis. The reaction mixture was poured into brine (50ml) and extracted with DCM (3 x 30ml). The combined extracts were washed with brine (2 x 20ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave a white gum. Chromatography (3% EtOAc/hex) gave the title compound (63) (740mg, 55%) as a colourless gum. [Found; C, 73.4; H, 8.66%; $C_{26}H_{36}O_3Si$ requires: C, 73.54; H, 8.55%]; ν_{max} (neat) cm^{-1}, 3062 (w), 2954 (w), 2855 (s), 1722 (vs, acetyl), 1602 (w), 1452 (s), 1276 (s), 1111 (vs); δ_h (270 MHz, $CDCl_3$), -0.17 (3H, s, Me), 0.16 (3H, s, Me), 0.91 (9H, s, ^tBu), 1.66 - 1.90 (4H, m, α-ether), 1.96 (2H, p, J= 6.5 Hz, $\underline{CH_2}$-CH_2-O), 2.78 (1H, dt, J= 14.0, 6.5 Hz, benzylic), 2.90 (2H, s, benzylic), 3.00 (1H, dt, J= 14.0, 6.5 Hz, benzylic), 4.35 (2H, t, J= 6.5 Hz, CH_2-O), 7.08 (4H, m, aromatic), 7.20 (2H, t, J= 7.7 Hz, *m*-benzoate), 7.54 (1H, tt, J= 7.3, 1.5 Hz, *p*-benzoate), 8.05 (2H, d, J= 7.7 Hz, benzylic); δ_C (67.8 MHz, $CDCl_3$), -0.4, 2.0 (q, Me), 20.6 (quaternary, ^tBu), 25.4 (t, benzylic), 27.8 (q, ^tBu), 29.4 (t, $\underline{CH_2}$-C-O), 36.8 (t, benzylic-C-O), 39.3 (t, $\underline{CH_2}$-benzylic), 45.1 (t, $\underline{CH_2}$-CH_2-O), 67.6 (t, CH_2-O), 127.9, 128.1, 130.5, 130.8, 131.6, 131.8, 132.8 (d, aromatics), 132.8 (quaternary, benzoate), 137.4, 137.8 (quaternary, 2 x aromatics), 168.8 (quaternary, carbonyl).

2-(3-Benzoylpropyl)-3,4-dihydronaphthalene (64):

To a solution of the TBDMS-ether (41) (340mg, 0.8mmol) in dry DCM (5ml), was added borontrifluoride etherate (200µl, 1.6mmol) in one aliquot. A colour change from clear to brown was noted and the resulting solution was left stirring overnight. Tlc analysis showed no starting material after the initial addition of the borontriflouride, but the isomerization of the alkene requires a minimum of 24 hrs. The reaction was quenched after 24 hrs with saturated sodium hydrogen carbonate solution and extracted with DCM (3 x 20ml). The organic extracts were combined, washed with brine (2 x 20ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to leave a brown oil.

Chromatography eluting with 3% EtOAc/Cyclhex gave the title compound (64) (225mg, 96%) as a colourless oil. B.p.60-64°C. Rf. 0.33 (5% EtOAC/Cyclhex); [Found; C, 82.0; H, 6.98%; $C_{20}H_{20}O_2$ requires: C, 82.15; H, 6.89 %]; ν_{max} (neat) cm^{-1}, 3061 (w), 3015 (w), 2928 (s), 2829 (s), 1716 (vs, carbonyl), 1274 (vs); δ_h (270 MHz, $CDCl_3$), 2.01 (2H, p, J= 7.5 Hz, CH_2), 2.27 (2H, t, J= 8.0 Hz, α-alkene), 2.35 (2H, t, J= 7.5 Hz, α-alkene), 2.82 (2H, t, J= 8.0 Hz, benzylic), 4.38 (2H, t, J= 7.5 Hz, CH_2-O), 6.27 (1H, s, alkene), 7.09 (4H, m, aromatics), 7.42 (2H, tt, J= 7.5, 1.0 Hz, *m*-benzoate), 7.55 (1H, tt, J= 8.2, 1.0 Hz, *p*-benzoate), 8.06 (2H, dd, J= 8.2, 1.0 Hz, o-benzoate); δ_c (67.8 MHz, $CDCl_3$), 26.7 (t, benzylic), 27.3, 28.1 (t, alkene), 33.9 (t, β-alkene), 64.6 (t, CH_2-O), 122.9 (d, alkene), 125.5, 126.2, 126.4, 127.1, 128.3, 129.5 (d, 6 x aromatics), 130.4 (quaternary, benzoate),132.8 (d, *o*-benzoate), 134.6, 134.7 (d, 2 x aromatics), 140.6 (quaternary, alkene). m/z E.I. (70eV), 292 (M^+, 18%), 187 (2%), 170 (M^+-$PhCO_2H$, 100%), 141 (70%), 128 (50%), 105 (45%); low E.I., 292 (90%), 170 (100%), 141 (3%).

2-(3-Phenylacetylpropyl)-3,4-dihydronaphthalene chromiumtricarbonyl (65):

Compound (64) (530mg, 1.81mmol), chromium hexacarbonyl (440mg, 2.0mmol) in DNBE (36ml), THF (12ml) and a few anti-bumping granules were heated at reflux for 36 hrs in the absence of light. The reaction was cooled and the solvent removed under high vacuum in the presence of silica (8g). Chromatography of the pre-absorbed product eluting with 20% EtOAc/Cyclhex gave the title compound (65) (410mg , 67%) as an unstable yellow gum; ν_{max} (neat) cm^{-1}, 3072 (w), 2956 (s), 1956 (vs, CO), 1866 (vs, CO), 1714 (vs, amide carbonyl); δ_h (270 MHz, $CDCl_3$), 1.98 (2H, p, J= 6.5 Hz, CH_2), 2.50 (6H, m, 3 x CH_2), 4.32 (2H, t, J= 6.5 Hz, CH_2-O), 5.25 (4H, m, aromatics), 5.90 (1H, s, alkene), 7.50 (3H, m, benzoate *m* + *p*), 8.07 (2H, d, J= 7.8 Hz, *o*-benzoate).

2-(3-N-Methylaminopropyl)-3,4-dihydronaphthalene (66):

The N-trifluoroacetyl compound (52) (300mg, 1.0mmol) potassium carbonate (420mg, 3.0mmol) methanol (30ml) and distilled water (10ml) were stirred vigorously for 24 hrs. At this point Tlc

analysis (10% EtOAc/Hex) showed starting material still present, however the solvent was removed *in vacuo* and the residue adsorbed onto silica and chromatography eluting with DEA [100:10:1] gave the title compound (66) (188mg, 92%) as a brown oil. B.p.188-190°C. Rf. 0.17 (DEA[100:10:1]); [Found; 201.1493%, $C_{14}H_{19}N$ requires: 201.1517, error of 2.4 ppm]; ν_{max} (neat) cm^{-1}, 3323 (brs, NH), 3015 (w), 2929 (s), 2881 (s), 1649 (w, alkene), 1486 (w), 1450 (w); δ_h (270 MHz, $CDCl_3$), 1.73 (2H, p, J= 7.0 Hz, CH_2), 1.80 (1H, brs, NH), 2.26 (4H, t, J= 8.0 Hz, α-alkene), 2.47 (3H, s, N-Me), 2.64 (2H, t, J= 7.0 Hz, CH_2-N), 2.82 (2H, t, J= 8.0 Hz, benzylic), 6.25 (1H, s, alkene), 6.99 (1H, d, J= 7.0 Hz, *o*-aromatic), 7.10 (3H, m, aromatics); δ_C (67.8 MHz, $CDCl_3$), 27.2, 27.5 (t, benzylic + α-alkene), 28.2 (t, CH_2-benzylic), 35.1 (t, CH_2), 36.2 (q, N-Me), 51.6 (t, CH_2-N), 122.4 (d, alkene), 125.3, 126.1, 126.4, 127.1 (d, 4 x aromatics), 134.4, 134.9 (quaternary, 2 x aromatics), 141.6 (quaternary, alkene); m/z E.I. (70eV), 201 (M^+, 28%), 170 (M^+-CH_3-NH_2, 14%), 141 (28%), 70 (40%), 44 (100%); low E.I. , 201 (100%), 70 (13%), 44 (15%).

2-(3-Bromopropyl)-2-(tertiarybutyldimethylsilyloxy)-1,2,3,4-tetrahydronaphthalene (67):

Carbon tetrabromide (18.6g, 56mmol) was added to a solution of triphenylphosphine (14.8g, 5mmol) in ether (70ml) at 0°C. The orange/brown suspension was allowed to stir vigorously for 1/2 hr before the alcohol (47) (9g, 28mmol) was added rapidly as a solution in ether (100ml). The mixture was left to stir overnight and then the reaction was diluted with hexane and filtered. The organic phase was adsorbed onto silica and purified by chromatography eluting with 1% EtOAc/Hex to give the title compound (67) (9.6g, 90%) as a clear oil; B.p.200°C @ 0.2mm Hg (decomposition); Rf. 0.74 (5% EtOAc/Hex); [Found; C, 59.4; H, 8.12; $C_{19}H_{31}BrOSi$ requires: C, 59.52; H, 8.15%]; ν_{max} (neat) cm^{-1}, 3018 (w), 2953 (s), 2855 (s), 1494 (w), 1254 (s), 1090 (s); δ_h (270 MHz, $CDCl_3$), -0.07 (3H, s, Me), 0.11 (3H, s, Me), 0.93 (9H, s, ^tBu), 1.54 (2H, m, CH_2), 1.67 (1H, dt, J= 13.1, 6.7 Hz, CH_2-benzylic), 2.78 (1H, d, J= 16.6 Hz, benzylic), 2.84 (1H, dt, J= 17.1, 6.7 Hz, benzylic), 3.29 (2H, m, CH_2-Br), 7.10 (4H, m, 4 x aromatics); δ_C (67.8 MHz, $CDCl_3$), -2.3 (q, Me), -2.0 (q, Me), 18.3 (quaternary, ^tBu), 25.8 (q, ^tBu), 27.0 (t, $\underline{CH_2}$.CH_2-Br), 27.1 (t, benzylic), 34.4 (t, CH_2-Br), 34.5 (t, $\underline{CH_2}$-C-O), 39.2 (t, Ph-$\underline{CH_2}$-C-O), 42.9 (t, CH_2-benzylic), 73.7 (quaternary, C-O), 135.1, 135.5 (quaternary, 2 x

aromatics), 125.7, 125.8, 128.5 129.3 (d, 4 x aromatics); m/z C.I. (iso-butane), 381:383 (M^+, 3%), 369 (2%), 325:327 (M^+-iso-propene, 27%), 283:285 (40%), 251:253 (M^+- $OSi(Me)_2{}^tBu$, 31%), 171 (100%).

2-(3-Bromopropyl)-3,4-dihydronaphthalene (68):

To a solution of the TBDMS-ether (67) (8.6g, 22.5mmol) in dry DCM (50ml) at 0°C under an Argon atmosphere was added boron trifluoride etherate (4.13ml, 33.7mmol) in one aliquot. The clear solution immediately turned pink and after 2 minutes it changed as rapidly again to a pale brown. The reaction was left stirring at R.T. for 96 hrs before being quenched by the slow addition of saturated sodium hydrogen carbonate solution (50ml) and stirred for a further 10 minutes. The organic phase was extracted with DCM (4 x 50ml) and the extracts combined, washed with brine (2 x 50ml), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to leave a pink oil. Chromatography eluting with 1-3% EtOAc/Hex gave the title compound (68) (4.62g, 81%) as a clear oil. B.p. 220°C @ 0.3 mmHg. Rf. 0.68 (5% EtOAc/Hex); [Found; C, 62.5; H, 6.12%; $C_{13}H_{15}Br$ requires: C, 62.15; H, 6.02%]; [Found; 252.0329, $C_{13}H_{15}Br$ requires: 252.0336, error of 0.7 ppm]; ν_{max} (neat) cm^{-1}, 3059 (w), 3013 (s), 2929 (s), 2828 (s), 1648 (w), 1485 (s), 1452 (s), 1434 (s); δ_h (270 MHz, $CDCl_3$), 2.12 (2H, p, J= 7.8 Hz, CH_2), 2.29 (2H, t, J= 8.0 Hz, CH_2-benzylic), 2.40 (2H, t, J= 7.5 Hz, CH_2-alkene), 2.87 (2H, t, J= 8.0 Hz, benzylic), 3.46 (2H, t, J= 6.9 Hz, CH_2-Br), 7.10 (4H, m, 4 x aromatics); m/z E.I.(70eV), 250:252 (M^+, 37%), 167 (27%), 143 (M^+-CH_3-CH_2Br, 100%), 129 (90%).

2-(3-Cyanopropyl)-3,4-dihydronaphthalene (69):

A solution of the crown-ether, 18-Crown-6 in acetonitrile (50ml,Saturated at 18°C) was added to the bromo compound (68) (4.6g, 18.33mmol) and solid potassium cyanide (3.6g, 55mmol) and then stirred vigorously for 24 hrs. The solvents was removed *in vacuo* and the residue adsorbed onto silica which was purified by chromatography eluting with 5-8% EtOAc/Hex to give the title compound (69)

(2.69g, 95%) as a pale yellow oil. B.p.195°C @ 0.3 mmHg; Rf. 0.19 (5% EtOAc/Hex); [Found; 197.1194, $C_{14}H_{15}N$ requires: 197.1204, error of 1.0 ppm]; ν_{max} (neat) cm^{-1}, 3015 (w), 2931 (s), 2245 (w, CN), 1648 (w, C=C, str.), 1485 (s), 1453 (s), 1426 (s); δ_h (270 MHz, $CDCl_3$), 1.91 (2H, p, J= 8.8 Hz, CH_2), 2.26 (2H, t, J= 8.1 Hz, CH_2-CN), 2.40 (4H, t, J= 7.1 Hz, α-alkene), 2.84 (2H, t, J= 8.1 Hz, benzylic), 6.30 (1H, s, alkene), 7.10 (4H, m, 4 x aromatics); m/z E.I. (70eV), 197 (M^+, 73%), 180 (43%), 169 (22%), 154 (47%), 141 (85%), 128 (100%). low E.I., 197 (100%), 180 (30%).

2-(4-Aminobutyl)-3,4-dihydronaphthalene (70):

To a stirred suspension of LAH (300mg, 7.51mmol) in ether at 0°C was slowly added the cyano-compound (69) (1.35g, 6.88mmol) as a solution in ether (30ml). The temperature was kept at 0°C, 5°C and at reflux for 5 mins before being cooled to 0°C and saturated sodium potassium tartrate solution added to decompose the excess LAH. The reaction mixture was extracted with ether (3 x 50ml). The organic extracts were combined, washed with brine (2 x 30ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to leave the title compound (70) (1.2g, 90%) as a brown oil. Rf. 0.17 (DEA 100:10:1); ν_{max} (neat) cm^{-1}, 3366 (br, NH_2), 3014 (w), 2926 (s), 1646 (w, C=C, str.), 1600 (w), 1485 (s), 1453 (s); δ_h (270 MHz, $CDCl_3$), 1.33 (2H, brs, NH_2, removed upon D_2O exchange), 1.52 (4H, m, CH_2-CH_2), 2.22 (4H, 2 x t, J= 8.0, 6.5 Hz, benzylic), 6.97 (1H, d, J= 7.0 Hz, o-aromatic), 7.10 (3H, m, aromatics).

2-(3-Chloropropyl)-2-(tertiarybutyldimethylsilyloxy)-1,2,3,4-tetrahydronaphthalene (70):

Thionyl chloride (88 µl, 1.2 mmol) was added to a solution of the alcohol (47) (320 mg, 1 mmol) and pyridine (97 µl, 1.2 mmol) in DCM (5 ml). After 2 hrs, brine was added and the organics were extracted with DCM, combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography eluting with 20% EtOAc: Hex to give the title compound (70) (188mg, 46%) as a clear oil. R_f. 0.47 (20% EtOAc/Hex); δ_h (270MHz, $CDCl_3$) -0.06 (3H, s, Me), +0.10 (3H, s, Me), 0.93 (9H, s, ^tBu), 1.60 (2H, t, J = 7.0 Hz, β-Cl), 1.84 (4H, m, α-C-O), 2.74 (1H, dt, J = 17.0, 6.5 Hz, benzylic), 2.82 (1H, d, J = 15.1 Hz, benzylic), 2.90 (1H, d, J= 15.1 Hz,

benzylic), 2.96 (1H, dt, J = 17.0, 6.5 Hz, benzylic), 3.97 (2H, m, α-Cl), 7.10 (4H, m, aromatics); δ_C (68.7MHz, $CDCl_3$) -2.3,-2.0 (q, Me), 18.3 (quaternary, ^tBu), 23.8 (t,β-Cl), 25.8 (q, ^tBu), 27.1 (t, benzylic), 34.4 (t, CH_2-C-O), 36.7 (t, benzylic-C-O), 42.8 (t, CH_2-benzylic), 62.7 (t, CH2-Cl), 73.7 (quatern. C-O), 125.7, 125.8, 128.5, 129.3, (d, aromatics), 135.1, 135.5 (quaternary, aromatics); m./z E.I. (70eV), 303 (M^+-HCl, 2%), 261 (25%), 239 (28%), 171 (52%), 129 (55%), 75 (100%).

2-(4-N-Trifluoroacetamidobutyl)-3,4-dihydronaphthalene (71):

TFAA (1.02ml, 7.2mmol) was added to a stirred solution of the primary amine (70) (1.2g, 6.0mmol) and pyridine (583μl, 7.2mmol) in DCM (25ml) at 0°C. After 40 minutes brine (10ml) was added and the reaction mixture extracted with ether (3 x 30ml). The organic extracts were combined, washed, dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was purified by chromatography eluting with 5% EtOAc/Hex and the crude material crystallized from EtOAc/Hex to give the title compound (71) (1.25g, 70%) as white crystalline solid. M.p. 58°C. Rf. 0.50 (10% EtOAc/Hex); [Found; C, 64.8; H, 6.10%; N, 4.69; $C_{16}H18NOF_3$ requires: C, 64.64; H, 6.10; N, 4.71%]; ν_{max} (Nujol) cm^{-1}, 3314 (w, NH), 2930 (s), 2853 (s), 1699 (vs, CO), 1558 (w, C=C, str.) 1206 (w), 1184 (w); δ_h (270 MHz, $CDCl_3$), 1.73 (4H, m, CH_2-CH_2), 2.34 (4H, m, 2 x α-alkene), 2.92 (2H, t, J= 8.2 Hz, benzylic), 3.50 (2H, q, J= 7.0 Hz, CH_2-N), 6.32 (1H, s, alkene), 6.37 (1H, brs, NH), 7.10 (1H, d, J= 7.0 Hz, o-aromatic), 7.24 (3H, m, 3 x aromatics); δ_C (100.4 MHz, $CDCl_3$), 24.4 (t, CH_2), 27.1, 28.1 (t, α-alkene), 28.5 (t, benzylic), 36.7 (t, $\underline{CH_2}$-CH_2-N), 39.8 (t, CH_2-N), 122.8 (d, alkene), 125.4, 126.3, 126.5, 127.2 (d, 4 x aromatics), 134.4, 134.7 (quaternary, aromatics), 141.0 (quaternary, alkene); m/z E.I. (70eV), 297 (M^+, 53%), 228 (M^+-CF_3, 5%), 210 (5%), 198 (2%), 183 (7%), 169 (2%), 155 (8%), 143 (75%), 129 (100%); low E.I., 297 (100%), 129 (10%), 100 (10%).

2-(4-N-Methyl-N-trifluoroacetamidobutyl)-3,4-dihydronaphthalene (72):

THF (8ml) was added to the amide (75) (250mg, 0.84mmol) and sodium hydride (60%) dispersion in mineral oil) (33mg, 1.1mmol) at 0°C. A vigorous reaction ensued that subsided within 15 minutes.

Methyliodide (8μl, 1.1mmol) was added dropwise to the reaction mixture, which was left to stand overnight. The reaction mixture was quenched by pouring it onto ice and extracting the mixture with ether (3 x 50ml). The organic extracts were combined, washed with brine (2 x 30ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to leave a gum. This was purified by chromatography eluting with 5% EtOAc/Hex to give the title compound (72) (235mg, 90%) as a clear oil. B.p.152°C (color change @ 132°C); Rf. 0.56 (10% EtOAc/Hex); [Found; 311.1520, $C_{17}H_{20}NOF_3$ requires: 311.1497, error of -2.3ppm]; ν_{max} (neat) cm^{-1}, 3378 (w, carbonyl overtone), 3016 (s), 2930 (s), 1694 (vs, carbonyl); δ_h (270 MHz, $CDCl_3$), 1.50 (4H, m, CH_2-CH_2), 2.20 (4H, m, α-alkene), 2.80 (2H, t, J= 8.0 Hz, benzylic), 2.95 (s, N-Me, rotamers), 3.05 (q, J= 1.6 Hz, N-Me, rotamers), 3.39 (2H, 2 x t, J= 8.0 Hz, CH_2-N, rotamers), 6.22 (1H, s, alkene), 6.95 (1H, d, J= 6.7 Hz, *o*-aromatic), 7.08 (3H, m, aromatics); m/z E.I. (70eV), 311 (M^+, 44%), 297 (M^+-CH_2, 17%), 242 (M^+-CF_3, 19%), 214 (M^+-$COCF_3$, 3%), 135 (M^+-N(Me)$COCF_3$, 9%), 143 (80%), 129 (100%); low E.I., 311 (100%), 297 (42%), 242 (25%), 142 (20%).

2-(4-N-p-Toluenesulfonylaminobutyl)-3,4-dihydronaphthalene (73):

To a solution of the primary amine (70) (307mg, 1.53mmol) and DMAP (375mg, 3.1mmol) in DCM (10ml) was added tosyl chloride (585mg, 3.1mmol) and the mixture stirred for 3 hrs. The solvent was removed *in vacuo* in the presence of silica to leave the products adsorbed. Chromatography eluting with 10% EtOAc/Hex gave the title compound (73) (140mg, 26%) as a pale yellow oil. B.p.90°C @ 2 mmHg (decomp.); Rf. 0.22 (10%EtOAc/Hex); [Found; 355.1593 $C_{21}H_{25}NO_2S$ requires: 355.1606, error of 1.3 ppm]; [Found; C, 70.6; H, 7.12%; N, 3.75; $C_{21}H_{25}NO_2S$ requires: C, 70.95; H, 7.09;N, 3.94%]; ν_{max} (neat) cm^{-1}, 3280 (vs, NH), 3090 (s), 2928 (s), 1426 (w), 1324 (s, asymm-SO2-str.), 1159 (s, symm-SO_2-str.), 1094 (w); δ_h (400 MHz, $CDCl_3$), 1.47 (4H, m, CH_2-CH_2), 2.12 (2H, m, α-alkene), 2.15 (2H, t, J= 8.0 Hz, CH_2-benzylic), 2.40 (3H, s, Me), 2.75 (2H, t, J= 8.0 Hz, benzylic), 2.95 (2H, q, J= 6.0 Hz, CH_2-NH), 4.66 (1H, t, J= 6 Hz, NH), 6.13 (1H, d, J= 7.0 Hz, *o*-aromatic), 7.10 (2H, m, *m* + *p* aromatics), 7.27 (2H, d, J= 8.0 Hz, *m*-SO_2), 7.74 (2H, d, J= 8.0 Hz, *o*-SO_2); δ_c (100.4 MHz, $CDCl_3$), 21.5 (q, Me), 24.3 (t, $\underline{CH_2}$-CH_2-alkene), 27.1 (t, $\underline{CH_2}$-CH_2-N), 28.1 (t, CH_2-alkene), 29.1 (t, CH2-

benzylic), 36.7 (t, benzylic), 43.1 (t, CH_2-N), 122.6 (d, alkene), 126.3, 126.1, 126.3, 126.4 (d, 4 x aromatics), 127.1, 129.7 (d, *o* + *p*-tol), 134.3, 134.7 (quaternary, aromatics), 136.6 (quaternary, alkene), 141.3, 143.4 (quaternary, 2 x tol); m/z E.I. (70eV), 355 (M^+, 3%), 328 (33%), 149 (50%), 57 (100%); C.I. (iso-butane), 356 (MH^+, 27%), 279 (30%), 253 (40%), 206 (40%), 154 (100%).

2-(4-N-Methyl-N-p-toluenesmlfonylaminobutyl)-3,4-dihydronaphthalene (74):

The chrominated sulfonamide (76) (55mg, 0.124mmol) was added as a solution in THF (5ml) to a suspension of potassium hydride (5mg, 0.124mmol) and DMPU (5ml). The mixture was maintained at -78°C and then allowed to reach R.T. overnight. Tlc analysis at this point (20% EtOAc/Hex) showed starting material, decomplexed starting material but no cyclisation products. Methyl iodide (8μl, 0.125mmol) was added and the reaction was stirred at R.T. for a further 24 hrs. The solution was then exposed to light and air to effect decomplexation and the solvent removed *in vacuo*. Chromatography eluting with 10% EtOAc/Hex gave the decomplexed sulfonamide (73) (26mg, 65%) and the title compound (74) (6mg, 15%) as a pale yellow oil; Rf. 0.54 (20%, EtOAc/Hex); [Found; 370.1848; $C_{22}H_{28}NO_2S$ requires: 370.1840, error of -2.1 ppm]; ν_{max}(neat) cm^{-1}, 2924 (vs), 1338 (s, asym-SO_2-str.), 1159 (vs, symm-SO_2-str.); δ_h (270 MHz, $CDCl_3$), 1.49 (4H, m, CH_2-CH_2), 2.20 (4H, 2 x t, J= 7.6, 7.6 Hz, benzylic-$\underline{CH_2}$ + alkene-$\underline{CH_2}$), 2.41 (3H, s, tol- CH_3), 2.70 (3H, s, Me-N), 2.77 (2H, t, J= 7.1 Hz, benzylic), 3.02 (2H, t, J=6.9 Hz, CH_2-N), 6.21 (1H, s, alkene), 6.95 (1H, d, J= 7.0 Hz, *o*-alkene), 7.04 (3H, m, aromatics), 7.26 (2H, d, J= 8.0 Hz, *m*-SO_2), 7.68 (2H, d, J= 8.0 Hz, *o*-SO_2); δ_C (100.4 MHz, $CDCl_3$), 21.5 (q, Me), 24.2 (t, $\underline{CH_2}$-CH_2-alkene), 27.0 (t, $\underline{CH_2}$-CH_2-N), 27.1 (t, CH_2-alkene), 28.2 (t, CH_2-benzylic), 34.6 (q, Me-N), 36.8 (t, benzylic), 49.9 (t, CH_2-N), 122.6 (d, alkene), 125.3, 126.1, 126.4, 127.2 (d, 4 x aromatics), 127.4, 129.6 (d, 2 x toluene), 134.3 (s, alkene), 134.7 (quaternary, C-CH_2), 134.8 (quaternary, alkene), 141.5, 143.2 (s, 2 x toluene); m/z C.I. (iso-butane), 370 (MH^+, 100%), 214 (45%); m/z +ve FAB (m-NBA), 370.1 (M^+, 100%), 214.1 (90%), 198.0 (50%), 141.1 (55%).

2-(4-N-Trifluoroacetamidobutyl)-3,4-dihydronaphthalene chromium tricarbonyl (75):

The amide (71) (140mg,0.47mmol), DNBE (18ml), THF (2ml) and chromiumhexacarbonyl (130mg, 0.57mmol) were refluxed for 24 hrs in the absence of light. The solvent was removed *in vacuo* and the product adsorbed onto silica and purified by chromatography eluting with 10% EtOAc/Hex to give the title compound (75) (144mg, 70%) as a yellow gum. Rf .0.2 (20% EtOAc/Hex); [Found; C, 53.0; H, 4.27%; N, 3.20 $C_{19}H_{18}CrNO_4$ requires: C, 52.66; H, 4.19; N, 3.23%]; (Found; 433.0594, $C_{19}H_{18}CrNO_4$ requires: 433.0593, error of -0.3 ppm]; δ_h (270 MHz, $CDCl_3$), 1.63 (4H, m), 2.28 (4H, m, α-alkene), 2.70 (2H, m, benzylic), 3.44 (2H, q, J= 6.9 Hz, CH_2-N), 5.34 (4H, m, 4 x aromatics), 5.93 (1H, s, alkene), 6.45 (1H, brs, NH); δ_C (100.4 MHz, $CDCl_3$), 23.9 (t, CH_2), 26.7, 26.8 (t, 2 x α-alkene), 28.0 (t, benzylic), 36.6 (t, $\underline{CH_2}$-CH_2-N), 39.6 (t, CH_2-N), 90.6, 90.8, 92.7, 93.8 (d, 4 x aromatics), 104.7, 106.7 (quaternary, 2 x aromatics), 119.0 (d, alkene), 146.0 (quaternary, alkene); m/z, +ve FAB, 433 (M^+, 52%), 349 (M^+- 3 x CO, 100%), 297 (15%).

2-(4-N-p-Toluenesulfonylaminobutyl)-3,4-dihydronaphthalenechromium tricarbonyl (76):

The sulfonamide (73) (140mg, 0.4mmol), chromiumhexacarbonyl (110mg, 0.5mmol), DNBE (18ml) and THF (2ml) were brought to reflux for 24 hrs in the absence of light. The solvents were removed in the presence of silica to leave the products pre-adsorbed. Chromatography eluting with 10% EtOAc/Hex gave two compounds. The first compound (17mg, 4%) appears to be the di-chrominated product (74), whereas the second is the title compound (76) (130mg , 67%), a bright yellow glue; Rf. 0.22 (30% EtOAc/Hex); [Found; 492.0932; $C_{24}H_{26}CrS$ requires: 492.0936, error of 0.8 ppm]; ν_{max} (neat) cm^{-1}, 3280 (br, NH), 309 (s), 2930 (s), 1953 (vs, CO), 1868 (vs, CO), 1485 (s); δ_h (270 MHz, $CDCl_3$), line broadening is evident due to paramagnetic chromium species present. 1.48 (4H, CH_2-CH_2), 2.10 (4H, CH_2-benzylic + CH_2-alkene), 2.41 (3H, s, Me), 2.68 (2H, benzylic), 2.92 (2H, CH_2-N), 4.86 (1H, t, J= 6.0 Hz, NH), 5.17 (2H, m, aromatics), 5.38 (2H, m, aromatics), 5.79 (1H, s, alkene), 7.28 (2H, d, J= 8.0 Hz, *m*-SO_2), 7.74 (2H, d, J= 8.0 Hz, *o*-SO_2); δ_C (100.4 MHz, $CDCl_3$), 21.4 (q, Me), 23.9 (t, CH_2), 26.6 (t, $\underline{CH}$-$_2CH_2$-N), 26.8 (t, CH_2-alkene), 28.7 (t, CH_2-benzylic), 36.5 (t,

benzylic), 43.0 (t, CH_2-N), 90.5, 90.7, 92.7, 93.7 (d, 4 x aromatics), 127.0, 129.7 (d, *o* + *m* aromatics), 136.7 (quaternary, alkene), 143.3, 146.3 (quaternary, 2 x tol); m/z, + ve FAB, 492.1 (M^+).

2-(4-N-Methyl-N-trifluoroacetamidobutyl)-3,4-dihydronaphthalenechromium tricarbonyl (77):

The amide (72) (200mg, 0.4mmol), chromiumhexacarbonyl (15mg ,0.71mmol), DNBE (18ml) and THF (2ml) were refluxed for 24 hrs in the absence of light . The mixture was cooled and the solvents removed *in vacuo* in the presence of silica to leave the product adsorbed. Chromatography eluting with 15% EtOAc/Hex gave starting material (72) (50mg, 25%) and the title compound (77) (86mg, 40%) as a yellow gum; Rf. 0.44 (10% ,EtOAc/Hex); ν_{max} (neat) cm^{-1}, 3120 (w), 2950 (w), 1951 (vs), 1865 (vs), 1694 (vs); m/z, +ve FAB (NBA), 447 (M^+, 44%), 419 (M-CO, 5%), 363 (M^+- 3 x CO, 100%), 311 (M^+-$Cr(CO)_3$, 7%), 141 (32%). The authenticity of this compound is proved since:

i) when subjected to O_2/hv it gives the parent compound.

ii) treatment with base then O_2/hν gives the corresponding amine [2-(4-N-methylaminobutyl)-3,4-dihydro naphthalene].

iii) treatment of the characterised amine (75) with base and methyl iodide gives the same product (77).

η^6-Chromium tricarbonyl-2-(3-N-methylpropylamino)-3,4-dihydronaphthalene (80):

Treatment of the acetamide complex (53) with a variety of aqueous base conditions with or without ultrasound or methyllithium as described previously[3] led to the isolation of the same product (80); ν_{max} (neat) cm^{-1} 3200, 2934, 1950, 1865, 1459; δ_h (270MHz, $CDCl_3$) 1.70-3.00 (aliphates) 2.55 (3H,s, methyl), 5.20-5.50 (4H, m, aromatics), 6.0 (1H, s, alkene); m/z ((+)FAB) 338 (MH^+, 100%), 253 (40), 202 (60), 149 (M-$(CH_3)_2$NMe, 95).

2-(4-N-Methylaminobutyl)-3,4-dihydronaphthalene (81):

A mixture of the chrominated acetamide (77) (86mg, 0.192mmol), potassium carbonate (186mg, 1.34mmol), methanol (4ml) and water (2ml) was sonicated in the absence of light for three days. The solvents were removed *in vacuo* and the organics were extracted with ether (3 x 20ml). The extracts were combined, washed with brine (2 x 20ml), dried ($MgSO_4$), and filtered. The filtered ether solution was then exposured to the atmosphere and light for 2 hrs then the ether was removed *in vacuo* and the residue was purified by chromatography eluting with DEA(100:10:1) to give the title compound (81) (18mg, 47%) as a yellow oil. Rf. 0.41 (DEA100:10:1); [Found; 201.1521, $C_{14}H_{19}N$ requires: 201.1517, error of -0.4 ppm]; δ_h (270 MHz, $CDCl_3$), 1.54 (2H, m, CH_2), 1.76 (2H, m, CH_2), 2.22 (4H, m, α-alkene), 2.48 (3H, s, Me), 2.61 (2H, t, J= 6.2 Hz, CH_2-N), 2.80 (2H, t, J= 8.1 Hz), 6.23 (1H, s, alkene), 7.10 (4H, m, aromatics). The structure of this compound is proven since when it was treated with pyridine and trifluoroactic anhydride in DCM it gave 2-(4-N-methyl-N-trifluoroacetamidobutyl)-3,4-dihydronaphthalene (51).

5-Methylcyclohex-2-enone (82):

This compound was prepared by following the procedure described by Schuda and Potlock [36] starting from 2-methoxytoluene; ν_{max} (neat) cm^{-1}, 2928 (s), 1677 (vs); δ_h (270 MHz, $CDCl_3$), 1.15 (3H, d, J= 7.0 Hz, Me), 1.76 (1H, qt, J= 7.0, 12.5 Hz, CH), 2.08 (1H, dqd, J= 14.0, 4.5, 0.7 Hz, 1 x CH_2-enone), 2.41 (3H, m, CH_2 + 1 x CH_2-enone), 5.95 (1H, dt, J= 10.0, 2.0 Hz, CH-CO), 6.95 (1H, dt, J= 10.0, 4.5 Hz, $\underline{CH}$-CH_2); δ_c (67.8 MHz, $CDCl_3$), 14.9 (q, Me), 25.4 (t, CH_2-alkene), 30.7 (t, CH_2), 41.5 (d, CH), 129.3 (d, CH-CH_2), 149.7 (d, $\underline{CH}$-CO), 202.3 (quaternary, carbonyl). Yield from 25ml of 2-methoxytoluene was 64%.

2(R,S),5(R,S)-5-(3-Methoxybenzyl)-2-methylcyclohexanone (84):

Finely ground magnesium (15.4g, 632mmol) in dry THF (50ml) containing a crystal of iodine was treated with a small amount of 3-methoxybenzyl chloride. As the reaction commenced it was heated and the rest of the chloride (31ml, 214mmol) added so as to keep the reaction at reflux. After the complete addition of the chloride the reaction mixture was heated at reflux for another 1 hr with the addition of THF (100ml). The reaction mixture was cooled to R.T. with the further addition of THF (100ml) and then cooled to -78°C. Copper(I) chloride (1.7g, 17.14mmol) was added along with ether (75ml) and this was maintained at -78°C for 40 minutes. The enone (82) (12.0g, 107mmol) was then added slowly as a solution in ether (25ml) with a further portion of ether (50ml). The reaction was maintained at -78°C for 4 hrs and then stirred at R.T. for 12 hrs.

At this point the reaction mixture had a very strong blue colour. Ammonium chloride solution (20ml) was added to quench the reaction and the remaining magnesium was removed by filtration. The remaining solution was diluted with brine (100ml) and extracted with ether (3 x 100ml). The combined organic extracts were washed with brine (50ml), dried ($MgSO_4$), filtered and the solvents removed *in vacuo* to leave a gum. This crystallised when triturated with hexane to give the title compound (84) (9.29g, 40%) as white crystals M.p.100-102°C; Rf. 0.14 (10% EtOAc/Hex); ν_{max} (neat) cm^{-1}, 2927 (s), 2858 (s), 1709 (vs), 1602 (s), 1490 (w), 1454 (w); [Found; C, 77.7; H, 8.91%; $C_{15}H_{20}O_2$ requires: C, 77.55; H, 8.68%]; δ_h (270 MHz, $CDCl_3$), 0.97 (3H, d, J= 6.3 Hz, Me), 1.00 - 2.65 (10H, m), 3.76 (3H, s, MeO), 6.69 (3H, m, 2 x o + p aromatics), 7.17 (1H, t, J= 8 Hz, m-aromatic); δ_C (67.8 MHz, $CDCl_3$), 14.3 (q, Me), 31.7, 34.7 (t, CH_2-CH_2), 42.0, 44.8 (d, CH x 2), 45.3 (t, benzylic), 48.1 (t, CH_2-CO), 55.1 (q, MeO), 111.3 (d, *o*-aromatic), 114.9 (d, o x 2), 121.5 (d, *p*-aromatic), 129.2 (d, *m*-aromatic), 141.0 (quaternary, C-CH_2), 159.6 (quaternary, C-OMe), 212.6 (quaternary, carbonyl); m/z C.I. (iso-butane), 250 (MNH_4^+).

Cis/trans 2(R,S),5(R,S)-5-(3-Methoxybenzyl)-2-methylcyclohexanone oxime (85):

Ketone (84) (7g,30mmol), sodium acetate (9.9g,120mmol), hydroxylamine hydrochloride (98.4g, 120mmol), methanol (75ml) and water (25ml) were stirred vigorously for 24 hrs. The solvent was removed *in vacuo* and the residue was diluted with brine (100ml) and extracted with EtOAc (4 x 50ml). The combined organic extracts were washed with water (100ml), dried ($MgSO_4$), and the solvent removed *in vacuo*. This gave a solid from which the title compound was obtained by crystallisation from hexane (85) (6.67g, 90%) as off white crystals. All data was obtained from the crystallized isomer. m.p.100-102°C; Rf. 0.31 (EtOAc); ν_{max} (neat) cm^{-1}, 3279 (brs, OH), 2925 (s), 1702 (w), 1658 (w), 1600 (s, C=N, str), 1487 (s), 1454 (s); [Found; C, 72.80; H,8.55; N, 5.46%; $C_{15}H_{21}NO_2$ requires: C, 72.84; H, 8.56; N, 5.66%]; For full analysis see appendix ; δ_h (400 MHz, $CDCl_3$),1.08 (3H, d, J= 6.4 Hz, Me), 1.19 (2H, m, one from each CH_2-CH_2), 1.42 (1H, t, J= 13.7 Hz, CH_2-C=N), 1.82 (3H, m, CH-benzylic + one from each CH_2-CH_2), 2.22 (1H, m, CH-C=N), 2.48 (1H, dd, J= 13.2, 7.8 Hz, benzylic), 2.70 (1H, dd, J= 13.2, 5.5 Hz, benzylic), 3.43 (1H, ddd, J= 13.7, 3.4, 2.2 Hz, CH_2-C=N), 3.79 (3H, s, MeO), 6.73 (3H, m, 2 x *o* + *p* aromatics), 7.19 (1H, t, J= 8.0 Hz, *m*-aromatic), 9.06 (1H, brs, OH); δ_c (100.4 MHz, $CDCl_3$), 16.2 (q, Me), 30.8 (t, CH_2-C=N), 31.5 + 35.1 (t, CH_2-CH_2), 37.5 + 39.5 (d, 2 x CH), 43.4 (t, benzylic), 55.1 (q, MeO), 111.3 (d, *o*-aromatic), 114.8 (d, *o* x 2), 121.6 (d, *p*-aromatic), 129.1 (d, *m*-aromatic), 141.6 (quaternary, C-CH_2), 159.5 (quaternary, C-OMe), 162.5 (quaternary, C=N); m/z E.I. (70eV), 247.1 (M^+, 13%), 231.1 (M^+-CH_4, 15%), 172.0 (10%), 122.1 (76%); low E.I. 247.1 (72%), 231.1 (100%), 122.1 (64%), 110.1 (42%); C.I. (iso-butene), 248 (MH^+).

Cis-4(R,S),7(S,R)-Hexahydro-4-(3-methoxybenzyl)-7-methyl-2H-azepine-2-one (87) and cis-3(S,R),6(R,S)-Hexahydro-6-(3-methoxybenzyl)-3-methyl-2H-azepine-2-one (86):

To a solution of the oxime (85) (10.8g,43.7mmol) in freshly distilled pyridine (100ml) was slowly added phosphorus oxychloride (4.5ml, 48.0mmol) at 0°C. The reaction was then allowed to stir at 0°C for a further 1/2 hr. The reaction mixture was poured into concentrated HCl (200ml) and water

(200ml) and then waiting for the product to form as an oil. The mixture was cooled and the extracted with EtOAc (5 x 100ml). The combined organic extracts were washed with water (2 x 100ml), dried ($MgSO_4$) filtered and the solvent removed *in vacuo* in the presence of silica to leave the products pre-adsorbed. Chromatography eluting with 0.5% MeOH/EtOAc gave the two title compounds (86) (1.86g,20%) as a 5:1 ratio of the two possible diastereoisomers and (87) (5.18g, 55%) as a 2:1 ratio of the two possible diastereoisomers. Both of the compounds were fractionally crystallized from EtOAc and EtOAc/Hex to produce pure samples of just the *cis* isomers that were to be used in subsequent reactions and for the collection of all data. Confirmation of the *cis* orientation and the absolute stereochemistry was from X-ray crystallography (see appendix). Compound (87): m.p.152°C. Rf. 0.31 (EtOAc); ν_{max} (neat) cm^{-1}, 2922, 2855, 1666 (s), 1595 (w), 1459 (s); [Found; C, 72.53; H, 8.72; N, 5.59%; $C_{15}H_{21}NO_2$ requires: C, 72.85; H, 8.56; N, 5.66%]; δ_h (400 MHz, $CDCl_3$), 1.23 (3H, d, J= 6.7 Hz, CH_3), 1.68 (4H, m, CH_2-CH_2), 2.17 (1H, m, CH-benzylic), 2.54 (2H, 2 x dd, J= 13.7, 9.5, 14.0, 6.4 Hz, 1 x CH_2-CO + 1 x benzylic), 2.77 (2H, 2 x dd, J= 13.7, 6.1, 14.0, 2.7 Hz, 1 x CH_2CO + 1 x benzylic), 3.52 (1H, m, CH-N), 3.80 (3H, s, MeO), 5.90 (1H, brs, NH, removed upon D_2O exchange), 6.75 (3H, m, 2 x *o* + *p*), 7.20 (1H, t, J= 7.9 Hz, *m*-aromatic); δ_c (100.4 MHz, $CDCl_3$), 22.3 (q, Me), 32.1 (t, CH_2), 33.0 (t, benzylic), 33.8 (d, CH-benzylic), 38.0 (t, CH_2-CH), 41.4 (t, CH_2-CO), 49.2 (d, CH-N), 55.1 (q, MeO), 111.2 (d, *o*-aromatic), 114.8 (d, *o* x 2 aromatic), 121.4 (d, *p*-aromatic), 129.2 (d, *m*-aromatic), 142.1 (q, C-CH_2), 159.5 (quaternary, C-OMe), 175.5 (quaternary, carbonyl); m/z E.I. (70eV), 247.1 (M^+, 100%), 188.1 (42%), 159.0 (44%), 126.1 (M^+-methoxybenzyl, 70%), 86.0 (27%); low E.I. 247.1 (100%). Compound (86): M.p. 130-132°C. Rf. 0.48 (EtOAc); ν_{max} (Nujol) cm^{-1}, 3200 (w), 2923 (vs), 2855 (vs), 1655 (s), 1596 (w); [Found; C, 72.85; H, 8.68; N, 5.60%; $C_{15}H_{21}NO_2$ requires: C, 72.85; H, 8.56; N, 5.66%]; δ_h (400 MHz, $CDCl_3$), 1.16 (3H, d, J= 7.0 Hz, Me), 1.74 (4H, m, CH_2-CH_2), 2.07 (1H, m, CH-benzylic), 2.54 (1H, m, CHCO), 2.56 (1H, dd, J= 13.7, 7.0 Hz, benzylic), 2.63 (1H, dd, J= 13.7, 8.5 Hz, benzylic), 2.95 (1H, dt, J= 15.0, 6.1 Hz, CH_2-N), 3.41 (1H, dd, J= 15.0, 5.2 Hz, CH_2-N), 3.79 (3H, s, CH_3O), 5.83 (1H, t, J= 6.1 Hz, NH), 6.74 (3H, m, 2 x *o* + *p*-aromatics), 7.21 (1H, t, J= 7.9 Hz, *m*-aromatic); δ_c (100.4 MHz, $CDCl_3$), 17.4 (q, Me), 27.4 (t, CH_2-CH), 33.5 (t, benzylic), 35.8 (t, CH_2-$CHCH_3$), 37.5, 38.2 (2 x d, 2 x CH), 44.3 (t, CH_2-N), 55.1 (q, CH_3O), 111.2 (d, *o*-aromatic), 114.6 (d, *o* x 2 aromatic), 121.2 (d, *p*-

aromatic), 129.5 (d, *m*-aromatic), 141.8 (quaternary, C-CH_2), 159.7 (quaternary, C-OMe), 179.9 (quaternary, carbonyl); m/z E.I. (70eV), 247.1 (M^+, 24%), 148.0 (17%), 126.1 (M^+-methoxybenzyl, 23%), 122.0 (100%); low E.I. 247.1 (100%), 217 (8%), 126.1 (12%), 122.1 (13%).

4(R,S),7(S,R)-Hexahydro-4-(3-methoxybenzyl)-1,7-dimethyl-2-azepinone (88):

THF (30ml) was added to the amide (87) (2.6g, 10.54mmol) and sodium hydride (60% dispersion in mineral oil) (844mg, 21.08mmol) at 0°C and the reaction mixture was stirred for 7 hrs. To the mixture was added methyl iodide (8.28ml, 52.7mmol) dropwise and the solution was left overnight at R.T., then it was poured onto ice. The reaction mixture was extracted with EtOAc (4 x 50ml). The combined organic extracts were washed with brine (2 x 50ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave a pale yellow oil. Krugelrohr distillation gave a clear oil which was crystallized from hexane to give the title compound (88) (2.7g, 100%) as clear crystals. M.p.49-50°C. Rf. 0.52 (EtOAc); ν_{max} (neat) cm^{-1}, 2927, 1639 (vs, amide), 1488 (s), 1457 (s), 1260 (s); [Found; C, 73.6; H, 9.20; N, 5.40%; $C_{16}H_{23}NO_2$ requires: C, 73.54; H, 8.87; N, 5.36%]; δ_h (400 MHz, $CDCl_3$). For full analysis see compound data appendix. 1.30 (3H, d, J= 7.3 Hz, Me), 1.45 (1H, m, 1 x $\underline{CH_2}$-CH), 1.66 (3H, m, 1 x CH_2-CH + CH_2-CCH_2), 1.90 (1H, m, CH), 2.44 (2H, 2 x dd, J= 14.1, 13.0, 9.7, 6.8 Hz, 1 x CH_2-CO + 1 x benzylic), 2.69 (2H, 2 x dd, J= 14.1, 13.0, 9.7, 6.8 Hz, 1 x CH_2-CO + 1 x benzylic), 2.95 (3H, s, N-Me), 3.60 (1H, m, CH-N), 3.78 (3H, s, CH_3-O), 6.72 (3H, m, *o* x 2 + *p* aromatic), 7.19 (1H, t, J= 7.7 Hz, *m*-aromatic); δ_c (100.4 Mhz, $CDCl_3$), 17.5 (q, Me), 29.0 (t, CH_2-CH), 31.9 (t, benzylic), 33.7 (q, N-Me), 35.4 (d, CH-benzylic), 42.8 (t, CH_2-CO), 43.0 (t, CH_2-CH-N), 54.6 (d, CH-N), 55.0 (q, CH_3-O), 111.2 (d, *o*-aromatic), 114.7 (d, o x 2), 121.4 (d, *p*-aromatic), 129.1 (d, *m*-aromatic), 141.6 (quaternary, C-CH_2), 159.4 (quaternary, C-OMe), 173.3 (quaternary, carbonyl); m/z E.I. (70eV), 261.1 (M^+,55%), 246.1 (M^+-CH_3, 13%), 188.1 (17%), 159.0 (28%), 140.1 (M^+-methoxybenzyl, 60%), 91 (32%), 58 (100%); low E.I. 261.1 (M^+, 100%), 140.1 (12%).

4(R,S),7(S,R)-4-(3-Methoxybenzyl)-7-(N-methyl-N-trifluoroacetamide)-octan-2-one (89):

Methyl lithium (470μl, 0.65mmol) was added to a solution of the dimethylazepinone (88) (170mg ,0.65mmol) in THF (5ml) at 0°C. This was left to stir at 0°C for 2 hrs during which time the colour changed from colourless to pale yellow. This solution was cooled to -23°C, TFAA (280μl, 1.97mmol) was added dropwise and the reaction was allowed to warm to R.T. and left for 1 hr. By now the solution had turned green and was poured into ice and extracted with EtOAc (4 x 20ml). The combined organic extracts were washed with brine (2 x 20ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Chromatography eluting with 30% EtOAc:Hex gave starting material (88) (52mg, 32%) and the title compound (89) (83mg,35%) as a colourless oil. B.p.160-170°C (Kugelrohr); Rf. 0.40 (30% EtOAc/Hex); ν_{max} (neat) cm^{-1}, 3410 (w, carbonyl overtone), 2931 (s), 1766 (s), 1689 (vs), 1636 (vs); δ_h (270 MHz, $CDCl_3$), 1.15 + 1.19 + 1.36 + 1.39 (3H, d, J= 7.0 Hz, CH_3-CH), 2.06 (3H, d, J=1.8 Hz, CH_3-CO), 2.20 - 2.70 (2H, m, benzylc), [2.76 (s) + 2.82 (q, J= 1.5 Hz), 3H, CH_3-N, rotamers], 3.80 (3H, d, J= 4.2 Hz), 3.93 + 4.48 (1H, m, CH-N, rotamers), 6.74 (3H, m, *o* + *p* aromatics), 7.21 (1H, m, *m*-aromatics); δ_C (100.4 MHz, $CDCl_3$), 18.9, 19.3 (q, CH_3-CH, rotamers), 20.5, 20.6 (q, CH_3-CO, rotamers), 26.9, 27.2 (q, CH_3-N, rotamers), 28.9, 29.4, 30.0, 30.4 (t, CH_2-CH_2, rotamers), 35.0, 35.1 (d, CH, rotamers), 40.0, 40.4 (t, benzylic, rotamers), 40.4, 40.5 (t, CH-CO, rotamers), 54.3, 54.8 (d, CH-N, rotamers), 55.2, 55.6 (q, CH_3-O, rotamers), 111.5, 112.0 (d, o-aromatics, rotamers), 113.9, 114.0 (d, o-aromatics, rotamers), 121.4, 121.7 (d, *p*-aromatics, rotamers), 129.4, 129.5 (d, m, rotamers), 129.4, 129.5 (d, m, rotamers), 141.6, 141.4 (s, m, rotamers), 157.2 (m, CF_3), 159.6, 159.7 (quternary, C-OMe, rotamers), 186.7, 187.0 (m,amide-carbonyl, rotamers), 208.2, 208.4 (quaternary, CO, rotamers); m/z E.I. (70eV), 373.3 (M^+, 8%), 357.2 (M^+-CH_4, 40%), 315 (64%), 246 (28%), 236 (100%), 188.1 (76%), 121 (85%); [Found; 373.1880, $C_{19}H_{26}NOF_3$ requires: 373.1865, error of 4.1 ppm].

2(R,S)-1'(S,R)-1,2-Dihydro-7-methoxy-4-methyl-2-[1'(N-methylamino)-1'-methylpropan-3'-yl]naphthalene (90):

An attempt to cyclise the final chrominated product (92) (65mg, 0.013mmol) by ultrasonication in methanol (5ml), water (0.5ml) and excess potassium carbonate for 72 hrs in the absence of light gave only the title compound (90) (20mg, 60%). Thus after the solvent was removed *in vacuo*, the chromium removed by exposure of this to air and light in ether and finally purification by chromatography eluting with DEA (100:10:1), the amine was obtained as an oil. Rf. 0.31 (DEA100:10:1); ν_{max} cm^{-1} (Nujol), 3333 (w, amine), 2925 (s), 2851 (s), 1726 (w), 1608 (s), 1500 (s); δ_h (270MHz, $CDCl_3$), 1.12 (3H, d, J= 5.8 Hz, CH_3-CH), 1.20 - 1.70 (4H, m, CH_2CH_2), 2.02 (3H, s, CH_3-alkene), 2.36 (1H, m, CH-N), 2.44 (3H, s, CH_3-N), 2.56 (1H, dd, J= 15.2, 10.0 Hz, benzylic), 2.65 (1H, m, CH-alkene), 2.82 (1H, dd, J= 15.2, 6.0 Hz, benzylic), 3.24 (1H, brs, amine [removed upon D_2O exchange]), 3.81 (3H, s, MeO), 5.60 (1H, s, alkene), 6.69 (1H, d, J= 3.5 Hz, *o*-aromatic), 6.71 (1H, dd, J= 8.0, 3.5 Hz, *o*-aromatic), 7.20 (1H, d, J= 8.0 Hz, *m*-aromatic); δ_C (100.4MHz, $CDCl_3$), 19.5 + 19.7 (q, CH_3-alkene + CH_3-CH), 21.8 (q, CH_3-N), 29.6 + 31.1 (t, CH_2CH_2), 33.8 + 34.0 (d, CH-N + CH-alkene), 35.3 (t, benzylic), 55.2 (q, MeO), 110.9 + 113.9 (d, o x 2), 123.8 (d, *m*-aromatic), 126.5 (d, alkene-CH), 128.8 + 131.2 (quaternary, 2 x aromatics), 137.1 (quaternary, alkene), 158.4 (quaternary, C-OMe); m/z E.I. (70eV), 259.2 (M^+, 15%), 244 (M^+-CH_3, 12%), 186.1 (McLafferty, 44%), 171.1 (20%), 149.0 (50%), 58.1 (100%). low eV, 259.2 (45%), 244.2 (20%), 186.1 (33%), 140.1 (40%), 58.1 (M^+-$CH_3C{=}NH_2$, 100%); [m/z Found; 259.1923, $C_{17}H_{25}NO$ requires: 259.1936, error of 4.8 ppm].

2(R,S),1'(S,R)-1,2-Dihydro-7-methoxy-4-methyl-2-[1'(N-methyl-N-trifluoroacetamido)-1'-methylpropan-3'-yl]naphthalene (91):

2 M Hydrochloric acid (0.5ml) was added to a solution of the ketone (89) (270mg,0.723mmol) in THF (10ml) and was heated at reflux for 1hr. The reaction was quenched by pouring into saturated sodium hydrogen carbonate solution. The aqueous phase was extracted with ether (3 x 20ml), the organic

extracts combined, washed with brine (2 x 10ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give an oil. Chromatography of the residue eluting with 20% EtOAc/Hex, gave starting material (89) (140mg,50%) and the title compound (91) (95mg, 45%) as a clear oil. Rf. 0.76, 0.72 (30% EtOAc/Hex); ν_{max} cm^{-1} (neat), 3368 (w, carbonyl overtone), 2927 (aromatics), 2856 (aliphatics), 1692 (vs, carbonyl), 1609 (s), 1250 (s), 1191 (s), 1143 (vs); δ_h (400 MHz, $CDCl_3$), 1.16 (3H, d, J= 6.6Hz, $\underline{CH_3}$-CH, rotamer), 1.23 (3H, d, J= 6.6Hz, $\underline{CH_3}$-CH, rotamer), 1.25 - 1.70 (4H, m, $\underline{CH_2}$-$\underline{CH_2}$), 2.02 (3H, d, J= 1.5 Hz, CH_3-alkene), 2.33 (1H, m, CH), 2.51 (1H, ddd, J= 14.6, 10.0, 2.5 Hz, benzylic), 2.78 (1H, ddd, J= 14.6, 6.3, 2.5 Hz, benzylic), [2.85 (s) + 2.92 (m), (3H, CH_3-N, rotamers)], 3.80 (3H, s, MeO), [3.97 (m) + 4.59 (m), (1H, CH-N, rotamers)], 5.55 (1H, s, alkene), 6.70 (1H, s, o-H), 6.72 (1H, dt, J= 8.3, 2.5 Hz, *m*-H), 7.14 (1H, dd, J= 8.3, 3.0 Hz, *o*-H); δ_c (100.4 MHz, $CDCl_3$), 17.4 (q, alkene CH_3), 19.0 + 19.4 (q, CH_3-CH, rotamers), 27.1 + 27.9 (q, CH_3-N, rotamers), 30.4 + 30.9 + 31.1 + 31.5 (t, CH_2-CH_2, rotamers), 33.6 (d, CH), 35.0 + 35.1 (t, benzylic, rotamers), 50.9 + 52.9 (d, CH-N, rotamers), 55.2 (q, MeO), 110.8 + 114.0 (d, *o*-aromatics), 123.9 + 124.0 (d, *m*-aromatics), 126.8 + 127.2 (d, alkene, rotamers), 128.6 + 128.7 (*s*, *p*-aromatics, rotamers), 156.9 (m, CF_3), 158.55 + 158.50 (s, C-OMe, rotamers); m/z E.I. (70eV), 355.2 (M^+, 12%), 186.1 (28%), 173.1 (M^+-butylamide, 100%), 158.1 (M-(butylamide + methyl), 18%); E.I. (low eV), 355.2 (M^+, 100%), 226.2 (7%), 186.1 (McLafferty, 40%), 173.1 (52%), 156.1 (22%); [m/z Found; 355.1725, $C_{19}H_{24}F_3NO_2$ reqiures: 355.1759, error of 9.4 ppm].

<u>2(R,S),1'(S,R)-1,2-Dihydro-7-methoxy-4-methyl-2-[1'(N-methyl-N-trifluoroacetamido)-1'-methylpropan-3'-yl]naphthalene chromiumtricarbonyl (92):</u>

DNBE (9ml), THF (1ml), chromium hexacarbonyl (61mg, 0.275mmol) and (91) (65mg, 0.183mmol) were heated at reflux refluxed in the absence of light for 24 hrs. The solvent was removed *in vacuo* in the presence of silica to leave the products adsorbed. Chromatography eluting with 10% EtOAc/Hex gave starting material (91) (23mg, 29%) and the title compound (92) (65mg, 100%) as a yellow oil. Rf. 0.35, 0.42 (30% EtOAc/Hex) (both stereoisomers due to the facial differentiation of the chromium); ν_{max} (cm^{-1}), 2942, 2855, 1953, 1867 (vs,CO), 1682 (vs, amide); δ_h (270MHz, $CDCl_3$),

1.10 - 1.70 (4H, m, CH_2CH_2), 1.23 (3H, m, $\underline{CH_3}CH$), 1.92 (3H, d (1:2), J= 2.5hz, CH_3-C), 2.40 - 2.90 (3H, m, benzylic + alkene), 2.90 (3H, d (5:3), J= 10 Hz, CH_3-N, rotamers), 3.72 (3H, d (1:2), J= 1.5 Hz, CH_3O), [4.61 (sex, J= 3 Hz) + 4.00 (m), (5:3), 1H, $\underline{CH}$-N, rotamers], 4.95 - 5.25 (2H, m, aromatics), 5.52 (1H, alkene), 5.61 (1H, t, J= 3 Hz, aromatic); δ_C (100.4 MHz, $CDCl_3$). Both α + β. 17.3 / 17.4 (q, CH_3-alkene, rotamers), 18.9 / 19.0 (q, CH_3, rotamers), 27.2 / 28.0 (q, CH_3-N, rotamers), 30.9 / 31.3 , 31.2 / 32.0 (t, CH_2-CH_2, rotamers), 31.0 / 33.5 (d, CH, rotamers), 34.4 / 35.3 (t, benzylic, rotamers), 50.6 / 52.6 (d, CH-N), 55.7 (q, CH_3O), 76.2 / 77.1 (d, *m*-aromatic), 77.4 / 79.1 (d, *o*-aromatic), 90.6 / 94.4 (d, *o* x 2), 97.2 / 104.6 (s, *p*-aromatic), 109.2 / 115.2 (s, *m*-aromatic), 128.5 / 128.7 (s, alkene), 130.0 / 130.4 (d, alkene), 141.8 / 143.0 (s, C-OMe), 156.9 (m, CF_3); FAB + in m-NBA. m/z 491.1 (M^+, 72%), 407.1(100%); [m/z FAB + in m-NBA. Found; 491.0973 $C_{22}H_{24}CrF_3NO_5$ requires: 491.1011, error of +7.8 ppm]; [Also found 492.101318, $C_{22}H_{24}{}^{52}CrF_3NO_5$ requires: 492.101309, error of 0.00 ppm]; [Found; C, 53.70; H, 2.60; N, 4.95%; $C_{22}H_{24}CrF_3NO_5$ requires: C, 53.77; H, 2.85; N, 4.92%].

2-(4-Aminobutyl)-3,4-dihydronaphthalene chromium tricarbonyl (95):

The chrominated amide (75) was treated with an excess of potassium carbonate and water in methanol for several hours until Tlc analysis indicated no starting material was remaining. The solvent was removed *in vacuo* and the reaction mixture extracted with ether (x 3). The combined organic extracts were washed with brine and dried ($MgSO_4$) to leave a residue that was quickly purified by chromatography eluting with DEA (100:10:1) to give the title compound as a yellow gum. Rf. 0.2 (DEA100:10:1); [Found; C, 60.2; H, 5.87; N, 4.21%; $C_{17}H_{19}CrNO_3$ requires: C, 60.53; H, 5.68; N, 4.15%]; ν_{max} (neat) cm^{-1}, 3340 (s, carbonyl overtone), 3013 (s), 2933 (vs), 1955 (vs, CO), 1852 (vs, CO), 1645 (w), 1457 (w); δ_h (270 MHz, $CDCl_3$), 1.50 (4H, m, CH_2-CH_2), 2.20 (4H, m, α-alkene), 2.50 (2H, m, CH_2-N), 2.52 (2H, m, benzylic), 5.22 (4H, m, aromatics), 5.82 (1H, s, alkene); δ_C (100.4 MHz, $CDCl_3$), 24.8 (t, CH_2), 27.1, 27.2 (t, 2 x α-alkene), 33.4 (t, benzylic), 37.4 (t, $\underline{CH_2}$-CH_2-N), 42.3 (t, CH_2-N), 90.7, 91.0, 92.8, 93.8 (d, 4 x aromatics), 105.3 (quaternary, C-alkene), 107.0 (quaternary,

C-CH_3), 118.3 (d, alkene), 147.4 (quaternary, alkene); m/z +ve FAB, 338 (M^+, 100%), 253 (55%), 202(55%).

3.3 **References.**

1. M.Sainsbury, C.S.Williams, A.Naylor, D.I.C.Scopes, *Tetrahedron Lett.*, **31**, 2763, (1990).

2. J.E. Baldwin, *J.Chem.Soc.,Chem.Commun.*, 734, (1976).

a) J.E. Baldwin J.Cutting, W.Dupont, L.Silberman, R.C.Thomas, *J.Chem.Soc.,Chem.Commun.*, 736, (1976).

b) J.E. Baldwin, *J.Chem.Soc.,Chem.Commun.*, 738, (1976).

3. J.E. Baldwin, L.I.Hruse, *J.Chem.Soc.,Chem.Commun.*, 233, (1977).

4. J.E. Baldwin, *J.Chem.Soc.,Chem.Commun*, 77, (1977).

5. H.B.Burgi, J.D. Dunitz, J.M. Lehn, G. Wipff, *Tetrahedron, **30**, 1563, (1974).*

6. H.H.Zeiss, P.J.Wheatley, H.J.S.Winkler, *'Benzoid-Metal Complexes', Ronald Press, New York,* (1966).

7. W.E.Silverthorn, *Adv. Organometallic Chem.*, **13**, 47, (1975).

8. B.Nicholls, M.C.Whitiny, *J. Chem. Soc.*, 551, (1959).

9. A.C.Knipe, S.J.McGuinness, W.E.Watts, *J.Chem.S.Perkin.Trans II*, 193, (1981).

10. G.R.Knox, D.G.Leppard, P.L.Pauson, W.E.Watts, *J.Organomet,Chem.*, **34**, 347, (1972).

11. K.K.Bhasin, W.G.Balkeen, P.L.Pauson, *J.Organomet.Chem.*, 204, C25, (1981).

12. C.C.Lee, M.Iqbal, U.S.Gill, R.G.Sutherland, *J.Organomet.Chem.*, **288**, 89, (1985).

13. C.A.L.Mahaffey, D.L.Pauson, *Inorg.Syn.*, **28**, 136, (1990).

14. M.Hudecek, S.Toma, *J.Organomet.Chem.*, **393**, 115, (1990).

a) M.Hudecek, S.Toma, *J.Organomet.Chem.*, **406**, 147, (1991).

b) D.Hrnciar, S.Toma, *J.Organomet.Chem.*, **413**, 161, (1991).

15. M. Sainsbury, M.F. Mahon, C.S. Williams, A. Naylor, D.I.Scopes, *Tetrahedron*, **47, 24**, 4195, (1991).

16. M.Nambu, D.C.Mohler, K.E.Hardcastle, K.F.Balderridge, J.S.Spegel, J.Am.Chem.Soc., **115**, 6138, (1993).

17. M.Sodeoka, M.Shibasaki, *Synthesis*, 643, (1993).

18. M.P.Rausch, *J.Org.Chem.*, **39**, 1787, (1974).

19. K.Otcle, E.Dotzauer, *J.Organomet.Chem.*, **30**, 211, (1971).

20. G.Carganico, P.DelButtero, S.Maiorana, G.Riccardi, *J.Chem.Soc.Chem.Comm.*, **864**, 989, (1978).

21. E.P.Kundig, *J.Organomet.Chem.*, ***286, 183, (1985).***

a) J.A.S.Howell, *J.Organomet.Chem.*, **294**, C1, (1985).

22. J.D.Selegue, K.A.Swardt, *J.Am.Chem.Soc.*, **115,** 6448, (1993).

23. G.B.M.Kostermans, *J.Organomet.Chem.*, **363**, 291, (1989).

24. M.Uemura, R.Miyake, Y.Hayashi, *J.Chem.Soc.Chem.Comm.*, 1696, (1991).

a*)* M.Umerura, *J.Org.Chem.*, **51**, 2859, (1986).

25. D.E.F.Gracy, W.R.Jackson, C.H.McMuller, N.Thompson, *J.Phys.Org.Chem(B),* 1197, (1969).

a) H.G.Schmalz, B.Millies, J.W.Bats, *Angew.Chem.Int.Ed.Eng.*, **31**, 631, (1992).

26. S.Top, G.Jaouen, C.Baldoli, P.Del.Buttero, S.Maiorana, *J.Organomet.Chem.*, **413**, 125, (1991).

27. M.Uemura, H.Nishimura, T.Hayashi, *Tetrahedron Lett.*, **34**, 107, (1993).

28. Y.Kondo, J.R.Green, J.Ho, *J.Org.Chem.*, **58**, 6182, (1993).

29. M.F.Semmelhack, H.T.Hali, M.Yoshituj, G.Clark, *J.Am,Chem.Soc.*, **97**, 1247, (1974).

30. G.Jaouen, R.Dabard, *Tetrahedron Lett.*, 1015, (1971).

31. M.F.Semmelhack, H.T.Hall.Jr., *J.Am.Chem.Soc.*, **96,** 7091, (1974).

32. A.C.Knipe, S.J.McGuinness, W.E.Watts, *J.Chem.Soc. Perkin Trans.1,* 193, (1981).

33. J.F.Bunnett, H.Herman, *J.Org.Chem.*, **36**, 4081, (1971).

34. S.I.Rosca, S.Rosca, *Rev.Chem., (Bucharest),* **25**, 461, (1964).

35. F.Rose-Munch, E.Rose, A.Semra, *J.Chem.Soc.Chem.Comm.*, 942, (1987).

36. F.Rose-Munch, E.Rose, A.Semra, *J.Organomet.Chem.*, **456**, C8, (1993).

37. M.E.Wright, *Chem.Abs,* **116**, 4619, (1991).

38. R.J.Card, W.S.Trayhanovsky, *J.Org.Chem.*, **45**, 2560, (1980).

39. C.Baidoli, P. Del Buttero, S.Maiorana, A.Papagni, *J.Chem.Soc.Chem.Comm.*, **48**, 3114, (1985).

40. R.D.Houghton, M.Voyle, R.Price, *J.Organomet.Chem.*, **259**, 183, *(1983).*

41. M.Uemura, H.Nishimura, K.Kamikawa, K.Nagagama, Y.Hayashi, *Tetrahedron Lett.*, **35**, 1909, (1994).

42. J.P.Gilday, D.A.Widdowson, *J.Chem.S.Chemm.Comm.*, 1235, (1986).

43. J.F.Bunnett, H.Hermann, *J.Org.Chem.*, **36,** 4081, (1971).

a) J.Schulz, J.Vogtle, *J.Chem.Soc.Perkin.Trans.II,* 2095, (1992).

44. F.Rose-Munch, J.P.Dukie, E.Rox, *Tetrahedron Lett.*, **31**, 2589, (1990).

45. J.P.Dukie,F.Rose-Munch, E.Rose, *J.Am.Chem.Soc.*, **115,** 6434, (1993).

46. M.Presson, U.Hacksell, I.Osoregh, *J.Chem.Soc.Perkin.Trans.I.*, 1453, (1991).

47. B.Ohlsson, C.Ullenius, *J.Organomet.Chem.*, **27**, C34, (1984).

48. M.F.Semmelhack, H.T.Hall.Jr., R.Farina, M.Yoshituji, G.Clark, T.M.Bargar, K.Hirotsu, J.Clardt, *J.Am.Chem.Soc.*, **101,** 3535, (1979).

49. S.Ostrowski, M.Mokosza, *J.Organomet.Chem.*, **367**, 95, (1989).

50. M.F.Semmelhack, *Comp.Org.Synth.*, **4**, 517, (1993).

51. M.F.Semmelhack, G.Clark, *J.Am.Chem.Soc.*, **99**, 1675, (1977).

a) M.F.Semmelhack, G.Clark, R.Farina, M.Saeman, *J.Am.Chem.Soc.*, **101**, 217, (1979).

52. E.P.Kundig, V.Desobry, D.P.Simmons, *J.Am.Chem.Soc.*, **105**, 6962, (1983).

53. S.Chamberlin, S.Wulff, *J.Am.Chem.Soc.*, **57**, 1855, (1992).

54. E.P.Kundig, A.F.Cunningham, Jr., P.Paglia, D.P.Simmons, G.Bernardelli, *Pure.Appl.Chem.*,**57**, 1855, (1985).

55. E.P.Kundig, A.F.Cunningham.Jr., P.Paglia, D.P.Simmons, *Helv.Chim.Acta.*, **73**, 386, (1990).

56. B.Ohlsson, C.Ullenius, *J.Organomet.Chem*, **350**, 35, (1988).

57. A.Solladie-Cavallo, G.Wipff, *Tetrahedron Lett.*, 3407, (1980).

58. F.van Meus, J.M. van der Toorn, H. van Bekkum, *J.Organomet.Chem.*, **113**, 341 and 353, (1976).

59. S.Laschat, R.Noe, M.Riedel, *Organometallics, 12, 3738, (1993).*

60. M.F.Semmelhack, L.Keller, Y.Thebtaranonth, *J.Am.Chem.Soc.*, **99**, 959, (1977).

61. M.F.Semmelhack, J.J.Harrison, Y.Thebtaranonth, *J.Org.Chem., 44, 3275, (1979).*

62. J.C.Boutonet, J.Levisalles, J.M.Normant, E.Rose, *J.Organomet.Chem., 255, C21, (1983).*

63. M.F.Semmelhack, A.Yamashitu, *J.Am.Chem.Soc.*, **102**, 5924, (1980).

64. F.Rose-Munch, L.Mignon, J.P.Schwarz, *Tetrahedron Lett., 32, 6323, (1991).*

65. E.P.Kundig, A.F.Cunningham, Jr., P.Paglia, D.P.Simmons, G.Bernardelli, *Helv.Chim.Acta.,* **73**, 386, (1990).

66. E.PKundig, M.Inage, G.Bernadinelli, *Organometallics*, **10**, 292, (1991).

67. E.P.Kundig, D.Amurrio, R.Liu, A.Ripn, *Synlett.,* 657, (1991).

68. E.P.Kundig, D.Ammurrio, A.Ripn, *J.Am.Chem.Soc.,* **113**, 9676, (1991).

69. J.A.Morley, N.F.Woolsey, *J.Org.Chem.*, **57**, 487, (1992).

70. H.G.Wey, P.Betz, H.Butenschow, *Chem.Ber.*, **124**, 465, (1991).

71. M.Uemura, R.Mikake, Y.Hayashi, *J.Chem.Soc.Chemm.Comm.*, 1696, (1991). S.J.Cook, *Tetrahedron Asymm.*, **1**, 817, (1990).

72. J.Schulz, M.Nieger, F.Vogtle, *J.Chem.Soc.Perkin Trans.II*, 2095, (1992).

73. V.N.Kalinir, I.Cherepanov, S.K.Moiseer, *Mendeleev.Comm.*, 43, (1993).

74. M.C.Senechal-Tocquer, D.Senechal, J.Y.LeBihan, D.Gentic, B.Caro, *J.Organomet.Chem.*, **433**, 261, (1992).

75. J.Lebibi, L.Pelinski, L.Macicjewski, J.Brocard, *Tetrahedron*, **46**, 6011, (1990).

76. H.G.Schmalz, J.Hollander, M.Arnold, G.Purner, *Tetrahedron Lett.*, **34**, 6259, (1993).

77. M.Uemura, H.Nishimura, T.Minami, Y.Hayashi, *J.Am.Chem.Soc.*, **113**, 5402, (1991).

78. M.C.Senechal-Tocquer, D.Senechal, J.Y.LeBihon, D.Gentric, B.Caro, *J.Organomet.Chem.*, **420**, 185, (1991).

79. S.G.Davies, M.R.Shipton, *Syn.lett.*, 25, (1991).

80. B.Caro, M.Senechal-Tocquer, D.Senechal, *Tetrahedront Lett.*, **34**, 7259, (1993).

81. M.T.Reetz, M.Sauerwald, *J.Organomet.Chem.*, **382**, 121, (1990).

82. S.J.Cook, S.G.Davies, C.L.Goodfellow, K.H.Sutton, D.Middlemins, A.Naylor, *Tetrahedron Asym.*, **1**, 33, (1990).

83. M.F. Semmelhack,W. Seufert & L. Keller, *J.Am.Chem.Soc.,* **102,** 6584, (1980).

84. S.Ganesh, K.M.Sathe, M.Nandi, P.Chakrabarti, A.Sarkar, *J.Chem.Soc.Chem.Comm.*, 224, (1993).

85. S.Ganesh, A.Sarkar, *Tetrahedron Lett.*, **32**, 1685, (1991).

86. M.Uemura, Y.Hayashi, Y.Hayashi, *Tetrahedron Asymm.*, **4**, 2291, (1993).

87. M.Brands, J.Bruckmann, C.Kruger, H.Butenschon, *J.Chem.Soc.Chem.Comm.*, 999, (1994).

88. M.Uemura, H.Oda, TMinami, M.Shiro, Y.Hayashi, *Organometallics*, **11**, 3705, (1992).

89. J.Brocard, L.Pelinski, L.Maciejewski, *Tetrahedron Lett.*, **44**, 6995, (1990).

90. C.Baldoli, P.Del Buttero, S.Maiorana, G.Zecchi, *Tetrahedron Lett.*, **34**, 2529, (1993).

91. M.Uemure, T.Minami, Y.Hayashi, *J.Chem.Soc.Chem.Comm.*, 1193, (1980).

91. S.Danishetsky, B.H.Migdalof, *J.Chem.Comms.*, 1107, (1969).

92. S.G.Davies, O.M.L.R.Fyrtado, D.Hepworth, T.Loveridge, *Syn.lett.*, 69, (1995).

93. H.T.Grimmins, D.K.Jung, *J.Am.Chem.Soc.*, *115*, 3146, (1993).

94. Hans-Gunther. Schmalz, S.Siegel, J.W.Bats, *Angew.Chem.Int.Ed.Engl.*,**34**, 2383, (1995).

95. S.F.Martin, Chi-yun Tu, *J.Org.Chem.*, **46**, 3763, (1981).

96. M.S.Newman, A.Arkell. T.Fukunaga, *J.Am.Chem.Soc.*, **82**, 2498, (1960).

97. O.Mitsunobu, *Synthesis*, 1, (1981).

98. I.M.Dordor, J.Mellor, *J.Chem.Soc., Perkin Trans.1*, 1247, (1984).

99. Nystrom & Brown, *J.Am.Chem.Soc* , **70**, 3738, (1948).

a) A.Hamlin & G.D.Weston, *J.Am.Chem.Soc.*, **71**, 2210, (1949).

100. A.G.Cook. *Enamines. p262 Mercel Dekker Inc., New York*, (1969).

101. T.Hiyama, M.Sawahata, *Chem. Letters*, 1237-1238 , (1983).

102. M.Ladlow, *PhD Thesis, University of Nottingham*, 191, (1985).

103. K.Omura, D.Swern, *Tetrahedron*, 1651,(1978).

104. J.Parikh, W.Doering, *J. m.Chem.Soc., 5507, (1967).*

105. H.C.Brown, W.R. Heydkamp, *J.Am.Chem.Soc.*, **86**, 3565,.(1964).

a) M.W.Rethke, K.R.Varma, H.C.Brown, *J.Am.Chem.Soc.*, 2870, (1966*).*

106. M.Lalonde, T.H.Chan, *Synthesis*, 817, (1986).

107. E.J.Corey, *J.Am.Chem.Soc.*, 6190, 1972 and 3455 (1981).

108. O.Mitsunobu, *Synthesis*, p6 the preparation of Octylamine.

109. Y.Ito, *Tetrahedron*, 5788, (1989).

110. D.R.Kelly, S.Roberts, R.Newton, *Synth. Commun.*, **9(4)**, 295-299, (1979).

111. H.Raymond, R.Helmuth, *J.Chem.Soc.*, 2348, (1926).

112. a) V.K.Aggarwal, S.Warren, *Tetrahedron Lett.*, **27**, 101, (1986).

b) V.K.Aggarwal, I.Coldham, S.McIntyre, F.M.Sansbury, Maria-Jesus.Ville, S.Warren, *Tetrahedron Lett.*, **29**, 4885, (1988).

c) I.Coldham, S.Warren, *Tetrahedron Lett.*, **30**, 5937, (1989).

d) I.Coldham, E.W.Collington, P.Hallett, S.Warren, *Tetrahedron Lett.*, **29**, 5321, (1988).

113. a) R.Davis, K.G.Untch, *J.Org.Chem.*, **46**, 2985, (1980).

b) A.Mizuno, Y.Hamada, T.Shioiri, *Synthesis*, 1007, (1980)

114. F.L.Cook, C.W.Bowers, C.L.Liotta, *J.Org.Chem.*, **39**, 3416, (1974).

114. S.G.Davis, T.J.Donohoe, A.M.Lister, *Tetrahedron Asym.*, **2**, 1685 and 1789, (1991).

115. H.C.Brown, C.F.Lane, *J.Am.Chem.Soc.*, 6660, (1970).

116. S.Harusawa, R.Yoneda, Y.Omori, T.Kurihara, *Tetrahedron Lett.*, **28**, 4189, (1987).

117. T.Mukhopadhyay, D.Seebach, *Helv.Chim.Acta.*, **65**, 385, (1982).

118. G.Jaouen, *Pure and Applied Chem.*, **58**, 597, 1986

119. I.Ryu, S.Murai, Y.Hatayuma, N.Sonoda, *Tetrahedron Lett.*, **37**, 3455, (1978).

120. H.O.House, L.J.Czuba, M.Gall, H.D.Olmsear, *J.Org.Chem.*, 2324, (1968).

121. Y.Ito, T.Hirao, T.Saegusa, *J.Org.Chem.*, **43**, 1011, (1978).

122. P.F.Schuda, S.J.Potluck, H.Ziffer, *Tetrahedron*, **43**, 463, (1987).

123. S.G.Davies, T.J.Donohoe, A.M.Lister, *Tetrahedron Asym.*, **2**, 1685, (1991).

124. T.Hiyama, M.Sawahata, Y.Kunsano, *Chem. Letters,* 611, (1985).

125. T.Hiyama, M.Obayashi, A.Nakamura, *Organometallics* ,**1**, 1249, (1982).

126. J.Malek , M.Cerny, *Synthesis,* 217, (1972).

127. Comprehensive Organic Synthesis, *2, Second Edn.*, 322, (1993).

128. S.Warren, I.Coldham, *Tetrahedron Lett.*, **43**, 5937, (1989).

a) Y.Tamaru , *J. Org.Chem.*, **53**, 5491, (1988).

129. I.Coldham, E.W.Collington, S.Wadau, *Tetrahedron Lett.*, **41,** 5321, (1988).

130. P.F.Schuda, S.J.Potlock, *Tetrahedron Lett.*, **43**, *463, (1987).*

131. *Organic Synthesis Collective Vol. II,* 606, (1943).

a) *Organic Synthesis Collective Vol. I,* 471, (1941).

b) *Organic Reactions Vol.* **41**, 241.

c) R.A.Benkeser, T.E.Johnston, *J.Am.Chem. Soc.,* 2220, (1966).

d) S.Danishefshy, B.H.Migdalof, *J.Chem.Soc.*, 2220, (1966).

e) A.Marfat, P.Helquist, *Tetrahedron Lett.*, 4217, (1978).

145. Z.V.Todres, E.A.Ionina, *J.Organomet.Chem.*, **43**, 197, (1993).

146. D.M.David, L.A.P.Kane-Maguire, S.G.Payne, *J.Chem.Soc.Dalton Trans.*, 293, (1994).

147. S.E.Gibson (nee Thomas), G.R.Jefferson, F.Prechtl, *J.Chem.Soc., Chem.Comms.*, 1535, (1995).

148. M.Uemura, *J.Organomet.Chem.*, **406**, 371, (1991).

Chapter 4

Appendices

Appendix i

X -Ray analysis of compound (86)

NOTE ON 95MS3

A crystal of approximate dimensions 0.2 x 0.2 x 0.2 mm was used for data collection.

Crystal data: $C_{15}H_{21}NO_2$, M = 247.3, monoclinic, a = 5.3616(6), b=10.252(1), c = 25.126(3)Å, β = 90.76(1)°, U = 1381.0 Å^3, space group $P2_1/c$, Z = 4, D_c = 1.19 gcm^{-3}, (μMo-K_α) = 0.7 cm^{-1}, $F(000)$ = 536. Data were measured at room temperature on a CAD4 automatic four-circle diffractometer in the range $2 \leq \theta \leq 24°$. 2567 reflections were collected of which 1100 were unique with $I \geq 2\sigma(I)$. Data were corrected for Lorentz and polarization but not for absorption.

In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions except in the case of H1 (attached to N1) which was located in the penultimate difference Fourier and refined at a distance of 0.96Å from the parent atom. As in the case of structure 95MS2, lattice neighbours related by an inversion centre are hydrogen bonded pairwise to each other. Typically, O2 of the molecule as presented interacts with H1 of the molecule generated via the operator *-x,2-y,-z*. (O2-H1, 1.93Å)

Final residuals after 10 cycles of least squares were R = 0.0445, R_w = 0.0406, for a weighting scheme of $w = 2.2766/[\sigma^2(F) + 0.000576(F)^2]$. Max. final shift/esd was 0.000. The max. and min. residual densities were 0.07 and -0.06 eÅ^{-3} respectively. Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles are given in Tables ... , ... and ... respectively. Tables of anisotropic temperature factors are available as supplementary data. The asymmetric unit is shown in Fig. ... , along with the labelling scheme used.

1. Sheldrick G.M., SHELX86, a computer program for crystal structure determination, University of Gottingen, 1986.
2. Sheldrick G.M., SHELX76, a computer program for crystal structure determination, University of Cambridge, 1976.

TABLE 1

Fractional atomic co-ordinates ($x10^4$) for 95MS3

	x	y	z
N(1)	2165(5)	11377(2)	47(1)
O(1)	4678(6)	14037(3)	3162(1)
O(2)	2166(4)	9548(2)	531(1)
C(1)	3330(7)	14014(4)	2698(1)
C(2)	1637(8)	15023(4)	2635(2)
C(3)	162(8)	15076(4)	2189(2)
C(4)	366(7)	14135(3)	1795(1)
C(5)	2049(6)	13121(3)	1852(1)
C(6)	3526(7)	13073(3)	2307(1)
C(7)	6463(9)	13038(4)	3248(2)
C(8)	2371(6)	12104(3)	1425(1)
C(9)	4721(6)	12311(3)	1092(1)
C(10)	5303(6)	11106(3)	753(1)
C(11)	3109(6)	10623(3)	433(1)
C(12)	3104(7)	12660(3)	-120(1)
C(13)	2811(6)	13679(3)	314(1)
C(14)	4686(6)	13588(3)	773(1)
C(15)	1706(8)	13035(3)	-630(1)

TABLE 3

Hydrogen fractional atomic co-ordinates ($x10^4$) and isotropic temperature factors ($Å^2$ $x10^3$) for 95MS3

	x	y	z	U
H(1)	750(34)	11044(28)	-148(10)	61(2)
H(21)	1501(8)	15683(4)	2904(2)	61(2)
H(31)	-1026(8)	15771(4)	2147(2)	61(2)
H(41)	-669(7)	14188(3)	1481(1)	61(2)
H(61)	4706(7)	12376(3)	2351(1)	61(2)
H(71)	7276(9)	13167(4)	3586(2)	61(2)
H(72)	7679(9)	13066(4)	2971(2)	61(2)
H(73)	5645(9)	12205(4)	3244(2)	61(2)
H(81)	2475(6)	11263(3)	1591(1)	61(2)
H(82)	940(6)	12130(3)	1191(1)	61(2)
H(91)	6087(6)	12413(3)	1340(1)	61(2)
H(101)	5856(6)	10418(3)	985(1)	61(2)
H(102)	6613(6)	11327(3)	512(1)	61(2)
H(121)	4862(7)	12616(3)	-186(1)	61(2)
H(131)	2978(6)	14525(3)	154(1)	61(2)
H(132)	1170(6)	13591(3)	458(1)	61(2)
H(141)	6319(6)	13709(3)	629(1)	61(2)
H(142)	4332(6)	14284(3)	1016(1)	61(2)
H(151)	2276(8)	13871(3)	-750(1)	61(2)
H(152)	-50(8)	13077(3)	-561(1)	61(2)
H(153)	2009(8)	12392(3)	-899(1)	61(2)

TABLE 4

Bond lengths (Å) for 95MS3

C(11)-N(1)	1.335(5)	C(12)-N(1)	1.471(5)
C(1)-O(1)	1.363(5)	C(7)-O(1)	1.416(6)
C(11)-O(2)	1.238(4)	C(2)-C(1)	1.384(6)
C(6)-C(1)	1.383(5)	C(3)-C(2)	1.365(6)
C(4)-C(3)	1.387(6)	C(5)-C(4)	1.383(5)
C(6)-C(5)	1.382(5)	C(8)-C(5)	1.508(6)
C(9)-C(8)	1.536(6)	C(10)-C(9)	1.536(6)
C(14)-C(9)	1.535(6)	C(11)-C(10)	1.499(5)
C(13)-C(12)	1.520(6)	C(15)-C(12)	1.524(6)
C(14)-C(13)	1.522(6)	H(1)-N(1)	0.960(2)
H(21)-C(2)	0.960	H(31)-C(3)	0.960
H(41)-C(4)	0.960	H(61)-C(6)	0.960
H(71)-C(7)	0.960	H(72)-C(7)	0.960
H(73)-C(7)	0.960	H(81)-C(8)	0.960
H(82)-C(8)	0.960	H(91)-C(9)	0.960
H(101)-C(10)	0.960	H(102)-C(10)	0.960
H(121)-C(12)	0.960	H(131)-C(13)	0.960
H(132)-C(13)	0.960	H(141)-C(14)	0.960
H(142)-C(14)	0.960	H(151)-C(15)	0.960
H(152)-C(15)	0.960	H(153)-C(15)	0.960

TABLE 5

Bond angles (°) for 95MS3

C(12)-N(1)-C(11)	126.7(4)	C(7)-O(1)-C(1)	117.8(4)
C(2)-C(1)-O(1)	115.1(4)	C(6)-C(1)-O(1)	125.1(4)
C(6)-C(1)-C(2)	119.7(4)	C(3)-C(2)-C(1)	119.8(4)
C(4)-C(3)-C(2)	120.5(5)	C(5)-C(4)-C(3)	120.4(4)
C(6)-C(5)-C(4)	118.6(4)	C(8)-C(5)-C(4)	121.7(4)
C(8)-C(5)-C(6)	119.6(4)	C(5)-C(6)-C(1)	121.0(4)
C(9)-C(8)-C(5)	113.2(3)	C(10)-C(9)-C(8)	111.4(3)
C(14)-C(9)-C(8)	113.4(4)	C(14)-C(9)-C(10)	113.4(3)
C(11)-C(10)-C(9)	113.5(3)	O(2)-C(11)-N(1)	120.5(4)
C(10)-C(11)-N(1)	119.0(4)	C(10)-C(11)-O(2)	120.5(4)
C(13)-C(12)-N(1)	111.8(3)	C(15)-C(12)-N(1)	107.3(4)
C(15)-C(12)-C(13)	112.0(4)	C(14)-C(13)-C(12)	115.3(4)
C(13)-C(14)-C(9)	116.8(4)	C(11)-N(1)-H(1)	117.0(20)
C(12)-N(1)-H(1)	116.3(19)	H(21)-C(2)-C(1)	120.1(3)
C(3)-C(2)-H(21)	120.1(3)	H(31)-C(3)-C(2)	119.7(3)
C(4)-C(3)-H(31)	119.8(3)	H(41)-C(4)-C(3)	119.8(3)
C(5)-C(4)-H(41)	119.8(3)	H(61)-C(6)-C(1)	119.5(3)
H(61)-C(6)-C(5)	119.5(3)	H(71)-C(7)-O(1)	109.5(3)
H(72)-C(7)-O(1)	109.5(3)	H(72)-C(7)-H(71)	109.5
H(73)-C(7)-O(1)	109.5(3)	H(73)-C(7)-H(71)	109.5
H(73)-C(7)-H(72)	109.5	H(81)-C(8)-C(5)	108.5(3)
H(82)-C(8)-C(5)	108.5(3)	H(82)-C(8)-H(81)	109.5
C(9)-C(8)-H(81)	108.5(3)	C(9)-C(8)-H(82)	108.6(3)
H(91)-C(9)-C(8)	106.7(3)	C(10)-C(9)-H(91)	106.8(3)
C(14)-C(9)-H(91)	104.4(3)	H(101)-C(10)-C(9)	108.4(2)
H(102)-C(10)-C(9)	108.4(3)	H(102)-C(10)-H(101)	109.5
C(11)-C(10)-H(101)	108.5(3)	C(11)-C(10)-H(102)	108.4(3)
H(121)-C(12)-N(1)	110.3(3)	C(13)-C(12)-H(121)	105.5(3)
C(15)-C(12)-H(121)	110.0(3)	H(131)-C(13)-C(12)	108.0(2)
H(132)-C(13)-C(12)	108.0(3)	H(132)-C(13)-H(131)	109.5
C(14)-C(13)-H(131)	108.0(3)	C(14)-C(13)-H(132)	108.0(3)
H(141)-C(14)-C(9)	107.6(3)	H(141)-C(14)-C(13)	107.6(3)
H(142)-C(14)-C(9)	107.6(3)	H(142)-C(14)-C(13)	107.6(3)
H(142)-C(14)-H(141)	109.5	H(151)-C(15)-C(12)	109.5(3)
H(152)-C(15)-C(12)	109.4(3)	H(152)-C(15)-H(151)	109.5
H(153)-C(15)-C(12)	109.5(3)	H(153)-C(15)-H(151)	109.5
H(153)-C(15)-H(152)	109.5		

TABLE 6

Selected non-bonded distances (Å) for 95MS3

Intramolecular:

O(2)-N(1)	2.235	C(9)-N(1)	3.098
C(10)-N(1)	2.444	H(102)-N(1)	2.642
H(121)-N(1)	2.017	C(13)-N(1)	2.477
H(132)-N(1)	2.553	C(15)-N(1)	2.413
H(152)-N(1)	2.594	H(153)-N(1)	2.595
O(2)-H(1)	2.409	C(11)-H(1)	1.967
C(12)-H(1)	2.083	C(15)-H(1)	2.430
C(2)-O(1)	2.319	H(21)-O(1)	2.478
C(6)-O(1)	2.438	H(61)-O(1)	2.656
H(71)-O(1)	1.957	H(72)-O(1)	1.957
H(73)-O(1)	1.958	C(10)-O(2)	2.380
H(101)-O(2)	2.440	H(21)-C(1)	2.042
C(3)-C(1)	2.378	C(4)-C(1)	2.756
C(5)-C(1)	2.406	H(61)-C(1)	2.035
C(7)-C(1)	2.380	H(72)-C(1)	2.610
H(73)-C(1)	2.610	H(31)-C(2)	2.021
C(4)-C(2)	2.389	C(5)-C(2)	2.780
C(6)-C(2)	2.393	C(3)-H(21)	2.025
H(31)-H(21)	2.323	H(41)-C(3)	2.042
C(5)-C(3)	2.404	C(6)-C(3)	2.747
C(4)-H(31)	2.041	H(41)-H(31)	2.341
C(6)-C(4)	2.378	C(8)-C(4)	2.526
H(82)-C(4)	2.575	C(5)-H(41)	2.038
C(8)-H(41)	2.692	H(61)-C(5)	2.034
H(81)-C(5)	2.029	H(82)-C(5)	2.029
C(9)-C(5)	2.542	H(91)-C(5)	2.636
C(14)-C(5)	3.111	H(142)-C(5)	2.720
C(7)-C(6)	2.823	H(72)-C(6)	2.765
H(73)-C(6)	2.748	C(8)-C(6)	2.499
H(81)-C(6)	2.639	C(7)-H(61)	2.523
H(72)-H(61)	2.324	H(73)-H(61)	2.298
C(8)-H(61)	2.643	H(72)-H(71)	1.568
H(73)-H(71)	1.568	H(73)-H(72)	1.568
H(91)-C(8)	2.032	C(10)-C(8)	2.538
C(11)-C(8)	2.949	C(14)-C(8)	2.567
H(142)-C(8)	2.680	H(82)-H(81)	1.568
C(9)-H(81)	2.053	C(10)-H(81)	2.617
C(9)-H(82)	2.054	C(11)-H(82)	2.725
C(14)-H(82)	2.725	H(101)-C(9)	2.053
H(102)-C(9)	2.053	C(11)-C(9)	2.539
C(12)-C(9)	3.176	C(13)-C(9)	2.605
H(141)-C(9)	2.042	H(142)-C(9)	2.042
C(10)-H(91)	2.033	H(101)-H(91)	2.234
C(14)-H(91)	2.003	H(141)-H(91)	2.230
H(142)-H(91)	2.281	C(12)-C(10)	2.944

C(13)-C(10)	3.149	C(14)-C(10)	2.567
H(141)-C(10)	2.742	H(102)-H(101)	1.568
C(11)-H(101)	2.020	C(11)-H(102)	2.020
C(14)-H(102)	2.625	C(12)-C(11)	2.509
H(121)-C(11)	2.741	C(13)-C(11)	3.151
H(131)-C(12)	2.033	H(132)-C(12)	2.034
C(14)-C(12)	2.571	H(141)-C(12)	2.754
H(151)-C(12)	2.054	H(152)-C(12)	2.054
H(153)-C(12)	2.054	C(13)-H(121)	2.003
C(14)-H(121)	2.610	C(15)-H(121)	2.060
H(151)-H(121)	2.352	H(153)-H(121)	2.352
H(141)-C(13)	2.031	H(142)-C(13)	2.031
C(15)-C(13)	2.525	H(151)-C(13)	2.692
H(152)-C(13)	2.735	H(132)-H(131)	1.568
C(14)-H(131)	2.035	H(141)-H(131)	2.297
H(142)-H(131)	2.289	C(15)-H(131)	2.577
C(14)-H(132)	2.035	H(142)-H(132)	2.299
H(142)-H(141)	1.568	H(152)-H(151)	1.568
H(153)-H(151)	1.568	H(153)-H(152)	1.568

Intermolecular:

O(2)-N(1a)	2.882	O(2)-H(1a)	1.923
C(11)-H(1a)	2.771	H(101)-O(1b)	2.588
H(71)-O(2c)	2.646		

Key to symmetry operations relating
designated atoms to reference atoms
at (x,y,z):

(A) -x,2.0-y,-z
(b) 1.0-x,-0.5+y,0.5-z
(c) 1.0-x,0.5+y,0.5-z

Appendix ii

X -Ray analysis of compound (87)

NOTE ON 95MS2

A crystal of approximate dimensions 0.4 x 0.4 x 0.3 mm was used for data collection.

Crystal data: $C_{14}H_{21}N_2O_2$, $M = 247.3$, triclinic, $a = 5.375(1)$, $b = 11.071(2)$, $c = 23.275(2)$Å, $\beta = 90.14(1)^\circ$, $U = 1385.0$ Å^3, space group $P2_1/c$, $Z = 4$, $D_c = 1.19$ gcm^{-3}, (Mo-K_α) = 12.4 cm^{-1}, $F(000) = 1242$. Data were measured at room temperature on a CAD4 automatic four-circle diffractometer in the range $2 \leq \theta \leq 24°$. 2568 reflections were collected of which 1375 were unique with $I \geq 2\sigma(I)$. Data were corrected for Lorentz and polarization but not for absorption.

The structure was solved by Direct methods and refined using the SHELX[1,2] suite of programs. In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant. Lattice neighbours related by an inversion centre are hydrogen bonded in pairs to each other. Typically, H1(attached to N1) of the molecule as presented interacts with O(2) of the molecule generated via the operator *-x,-y,-z.* (H1-O2, 1.99 Å).

Final residuals after 10 cycles of least squares were $R = 0.0406$, $R_w = 0.0390$, for a weighting scheme of $w = 3.2411/[\sigma^2(F) + 0.000176(F)^2]$. Max. final shift/esd was 0.000. The max. and min. residual densities were 0.06and -0.05 eÅ^{-3} respectively. Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles are given in Tables ... , ... and ... respectively. Tables of anisotropic temperature factors are available as supplementary data. The asymmetric unit is shown in Fig. ... , along with the labelling scheme used.

1. Sheldrick G.M., SHELX86, a computer program for crystal structure determination, University of Gottingen, 1986.
2. Sheldrick G.M., SHELX76, a computer program for crystal structure determination, University of Cambridge, 1976.

TABLE 1

Fractional atomic co-ordinates ($x10^4$) for 95MS2

	x	y	z
N(1)	-2577(4)	952(2)	-281(1)
O(1)	-5196(4)	3976(2)	-3233(1)
O(2)	205(3)	1358(1)	411(1)
C(1)	-3669(5)	3942(2)	-2761(1)
C(2)	-2029(5)	4896(2)	-2712(1)
C(3)	-397(5)	4940(2)	-2257(1)
C(4)	-398(5)	4027(2)	-1847(1)
C(5)	-2044(4)	3073(2)	-1889(1)
C(6)	-3665(4)	3033(2)	-2354(1)
C(7)	-6971(6)	3040(3)	-3298(1)
C(8)	-2199(4)	2112(2)	-1432(1)
C(9)	-4500(4)	2237(2)	-1051(1)
C(10)	-4767(4)	1179(2)	-638(1)
C(11)	-1689(5)	1650(2)	138(1)
C(12)	-2989(4)	2837(2)	258(1)
C(13)	-2782(5)	3681(2)	-264(1)
C(14)	-4665(4)	3456(2)	-744(1)
C(15)	-1919(6)	3417(2)	795(1)

TABLE 2

Anisotropic temperature factors (Å x10^3) for 95MS2

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	56(1)	33(1)	45(1)	-1(1)	-6(1)	11(1)
O(1)	75(1)	100(1)	62(1)	30(1)	-21(1)	-12(1)
O(2)	67(1)	55(1)	58(1)	-11(1)	-20(1)	24(1)
C(1)	51(2)	65(2)	48(1)	10(1)	-3(1)	3(1)
C(2)	64(2)	60(2)	68(2)	23(1)	2(2)	-3(2)
C(3)	60(2)	59(2)	81(2)	8(2)	0(2)	-16(1)
C(4)	50(2)	63(2)	55(1)	0(1)	-7(1)	-4(1)
C(5)	41(1)	47(1)	42(1)	0(1)	1(1)	5(1)
C(6)	48(1)	52(1)	47(1)	4(1)	-1(1)	-3(1)
C(7)	69(2)	110(2)	58(2)	6(2)	-18(1)	-4(2)
C(8)	46(1)	49(1)	42(1)	1(1)	-2(1)	10(1)
C(9)	37(1)	46(1)	45(1)	4(1)	-4(1)	8(1)
C(10)	48(1)	45(1)	46(1)	1(1)	-3(1)	1(1)
C(11)	49(1)	40(1)	39(1)	1(1)	-1(1)	7(1)
C(12)	48(1)	45(1)	46(1)	-5(1)	-2(1)	12(1)
C(13)	54(2)	34(1)	61(1)	-5(1)	3(1)	10(1)
C(14)	47(1)	48(1)	52(1)	8(1)	3(1)	14(1)
C(15)	87(2)	57(2)	63(2)	-15(1)	-9(2)	24(1)

TABLE 3

Hydrogen fractional atomic co-ordinates ($x10^4$) and isotropic temperature factors ($Å^2$ $x10^3$) for 95MS2

	x	y	z	U
H(1)	-1773(43)	261(22)	-349(9)	58(7)
H(21)	-2030(5)	5528(2)	-2994(1)	61(2)
H(31)	748(5)	5602(2)	-2223(1)	61(2)
H(41)	754(5)	4060(2)	-1531(1)	61(2)
H(61)	-4796(4)	2367(2)	-2393(1)	61(2)
H(71)	-7914(6)	3171(3)	-3643(1)	61(2)
H(72)	-8072(6)	3038(3)	-2974(1)	61(2)
H(73)	-6130(6)	2276(3)	-3321(1)	61(2)
H(81)	-2246(4)	1336(2)	-1615(1)	61(2)
H(81)	-744(4)	2166(2)	-1193(1)	61(2)
H(91)	-5903(4)	2214(2)	-1307(1)	61(2)
H(101)	-5099(4)	465(2)	-859(1)	61(2)
H(102)	-6149(4)	1340(2)	-389(1)	61(2)
H(121)	-4723(4)	2686(2)	325(1)	61(2)
H(131)	-1145(5)	3590(2)	-422(1)	61(2)
H(132)	-2997(5)	4496(2)	-132(1)	61(2)
H(141)	-6298(4)	3519(2)	-581(1)	61(2)
H(142)	-4445(4)	4077(2)	-1027(1)	61(2)
H(151)	-2756(6)	4168(2)	867(1)	61(2)
H(152)	-175(6)	3565(2)	741(1)	61(2)
H(153)	-2149(6)	2886(2)	1117(1)	61(2)

TABLE 4

Bond lengths (Å) for 95MS2

C(10)-N(1)	1.461(4)	C(11)-N(1)	1.331(4)
C(1)-O(1)	1.369(4)	C(7)-O(1)	1.417(4)
C(11)-O(2)	1.242(3)	C(2)-C(1)	1.381(4)
C(6)-C(1)	1.382(4)	C(3)-C(2)	1.373(4)
C(4)-C(3)	1.391(4)	C(5)-C(4)	1.381(4)
C(6)-C(5)	1.388(4)	C(8)-C(5)	1.507(5)
C(9)-C(8)	1.529(5)	C(10)-C(9)	1.522(5)
C(14)-C(9)	1.529(5)	C(12)-C(11)	1.516(5)
C(13)-C(12)	1.537(5)	C(15)-C(12)	1.517(5)
C(14)-C(13)	1.527(5)	H(1)-N(1)	0.893(25)
H(21)-C(2)	0.960	H(31)-C(3)	0.960
H(41)-C(4)	0.960	H(61)-C(6)	0.960
H(71)-C(7)	0.960	H(72)-C(7)	0.960
H(73)-C(7)	0.960	H(81)-C(8)	0.960
H(81)-C(8)	0.960	H(91)-C(9)	0.960
H(101)-C(10)	0.960	H(102)-C(10)	0.960
H(121)-C(12)	0.960	H(131)-C(13)	0.960
H(132)-C(13)	0.960	H(141)-C(14)	0.960
H(142)-C(14)	0.960	H(151)-C(15)	0.960
H(152)-C(15)	0.960	H(153)-C(15)	0.960

TABLE 5

Bond angles (°) for 95MS2

C(11)-N(1)-C(10)	127.2(3)	C(7)-O(1)-C(1)	117.9(3)
C(2)-C(1)-O(1)	115.3(3)	C(6)-C(1)-O(1)	124.7(3)
C(6)-C(1)-C(2)	120.0(3)	C(3)-C(2)-C(1)	119.9(3)
C(4)-C(3)-C(2)	120.1(3)	C(5)-C(4)-C(3)	120.5(3)
C(6)-C(5)-C(4)	118.7(3)	C(8)-C(5)-C(4)	121.7(3)
C(8)-C(5)-C(6)	119.5(3)	C(5)-C(6)-C(1)	120.8(3)
C(9)-C(8)-C(5)	113.1(3)	C(10)-C(9)-C(8)	111.9(3)
C(14)-C(9)-C(8)	113.5(3)	C(14)-C(9)-C(10)	112.2(3)
C(9)-C(10)-N(1)	114.5(3)	O(2)-C(11)-N(1)	121.1(3)
C(12)-C(11)-N(1)	118.3(3)	C(12)-C(11)-O(2)	120.6(3)
C(13)-C(12)-C(11)	110.3(3)	C(15)-C(12)-C(11)	110.2(3)
C(15)-C(12)-C(13)	111.5(3)	C(14)-C(13)-C(12)	115.5(3)
C(13)-C(14)-C(9)	116.6(3)	C(10)-N(1)-H(1)	115.8(15)
C(11)-N(1)-H(1)	117.0(15)	H(21)-C(2)-C(1)	120.1(2)
C(3)-C(2)-H(21)	120.1(3)	H(31)-C(3)-C(2)	119.9(3)
C(4)-C(3)-H(31)	119.9(2)	H(41)-C(4)-C(3)	119.7(2)
C(5)-C(4)-H(41)	119.7(2)	H(61)-C(6)-C(1)	119.6(2)
H(61)-C(6)-C(5)	119.6(2)	H(71)-C(7)-O(1)	109.5(2)
H(72)-C(7)-O(1)	109.5(2)	H(72)-C(7)-H(71)	109.5
H(73)-C(7)-O(1)	109.5(2)	H(73)-C(7)-H(71)	109.5
H(73)-C(7)-H(72)	109.5	H(81)-C(8)-C(5)	108.6(2)
H(81)-C(8)-C(5)	108.6(2)	H(81)-C(8)-H(81)	109.5
C(9)-C(8)-H(81)	108.6(2)	C(9)-C(8)-H(81)	108.6(2)
H(91)-C(9)-C(8)	105.8(2)	C(10)-C(9)-H(91)	107.2(2)
C(14)-C(9)-H(91)	105.5(2)	H(101)-C(10)-N(1)	108.2(2)
H(101)-C(10)-C(9)	108.2(2)	H(102)-C(10)-N(1)	108.2(2)
H(102)-C(10)-C(9)	108.2(2)	H(102)-C(10)-H(101)	109.5
H(121)-C(12)-C(11)	109.1(2)	C(13)-C(12)-H(121)	107.8(2)
C(15)-C(12)-H(121)	107.8(2)	H(131)-C(13)-C(12)	107.9(2)
H(132)-C(13)-C(12)	107.9(2)	H(132)-C(13)-H(131)	109.5
C(14)-C(13)-H(131)	107.9(2)	C(14)-C(13)-H(132)	108.0(2)
H(141)-C(14)-C(9)	107.7(2)	H(141)-C(14)-C(13)	107.7(2)
H(142)-C(14)-C(9)	107.7(2)	H(142)-C(14)-C(13)	107.7(2)
H(142)-C(14)-H(141)	109.5	H(151)-C(15)-C(12)	109.5(2)
H(152)-C(15)-C(12)	109.5(2)	H(152)-C(15)-H(151)	109.5
H(153)-C(15)-C(12)	109.5(2)	H(153)-C(15)-H(151)	109.5
H(153)-C(15)-H(152)	109.5		

TABLE 6

Selected non-bonded distances (Å) for 95MS2

Intramolecular:

O(2)-N(1)	2.240	C(8)-N(1)	2.977
H(81)-N(1)	2.701	C(9)-N(1)	2.509
H(101)-N(1)	1.983	H(102)-N(1)	1.983
C(12)-N(1)	2.445	H(121)-N(1)	2.648
C(13)-N(1)	3.023	C(2)-O(1)	2.323
H(21)-O(1)	2.481	C(6)-O(1)	2.438
H(61)-O(1)	2.653	H(71)-O(1)	1.958
H(72)-O(1)	1.959	H(73)-O(1)	1.959
H(1)-O(2)	2.392	C(12)-O(2)	2.398
C(15)-O(2)	2.703	H(152)-O(2)	2.570
H(153)-O(2)	2.678	C(10)-H(1)	2.017
H(101)-H(1)	2.156	C(11)-H(1)	1.910
H(21)-C(1)	2.039	C(3)-C(1)	2.383
C(4)-C(1)	2.759	C(5)-C(1)	2.408
H(61)-C(1)	2.036	C(7)-C(1)	2.387
H(72)-C(1)	2.616	H(73)-C(1)	2.616
H(31)-C(2)	2.030	C(4)-C(2)	2.395
C(5)-C(2)	2.782	C(6)-C(2)	2.393
C(3)-H(21)	2.031	H(31)-H(21)	2.332
H(41)-C(3)	2.045	C(5)-C(3)	2.408
C(6)-C(3)	2.755	C(4)-H(31)	2.047
H(41)-H(31)	2.347	C(6)-C(4)	2.382
C(8)-C(4)	2.523	H(81)-C(4)	2.568
C(5)-H(41)	2.036	C(8)-H(41)	2.688
H(61)-C(5)	2.041	H(81)-C(5)	2.029
H(81)-C(5)	2.029	C(9)-C(5)	2.533
H(91)-C(5)	2.656	C(14)-C(5)	3.047
H(142)-C(5)	2.634	C(7)-C(6)	2.822
H(72)-C(6)	2.770	H(73)-C(6)	2.741
C(8)-C(6)	2.502	H(81)-C(6)	2.658
C(9)-C(6)	3.191	C(7)-H(61)	2.519
H(72)-H(61)	2.338	H(73)-H(61)	2.276
C(8)-H(61)	2.650	H(72)-H(71)	1.568
H(73)-H(71)	1.568	H(73)-H(72)	1.568
H(91)-C(8)	2.016	C(10)-C(8)	2.529
H(101)-C(8)	2.746	C(14)-C(8)	2.557
H(142)-C(8)	2.660	H(81)-H(81)	1.568
C(9)-H(81)	2.048	H(91)-H(81)	2.309
C(10)-H(81)	2.656	C(9)-H(81)	2.048
C(10)-H(81)	2.748	C(14)-H(81)	2.754
H(101)-C(9)	2.038	H(102)-C(9)	2.038

C(13)-C(9)	2.599	H(131)-C(9)	2.761
H(141)-C(9)	2.037	H(142)-C(9)	2.037
C(10)-H(91)	2.026	H(101)-H(91)	2.240
H(102)-H(91)	2.349	C(14)-H(91)	2.011
H(141)-H(91)	2.234	H(142)-H(91)	2.299
C(11)-C(10)	2.501	C(12)-C(10)	2.937
C(13)-C(10)	3.093	C(14)-C(10)	2.533
H(141)-C(10)	2.722	H(102)-H(101)	1.568
C(11)-H(102)	2.712	H(121)-H(102)	2.360
C(14)-H(102)	2.610	H(121)-C(11)	2.042
C(13)-C(11)	2.505	H(131)-C(11)	2.530
C(15)-C(11)	2.488	H(152)-C(11)	2.670
H(153)-C(11)	2.670	H(131)-C(12)	2.048
H(132)-C(12)	2.048	C(14)-C(12)	2.591
H(141)-C(12)	2.745	H(151)-C(12)	2.048
H(152)-C(12)	2.048	H(153)-C(12)	2.048
C(13)-H(121)	2.047	C(14)-H(121)	2.631
C(15)-H(121)	2.028	H(151)-H(121)	2.322
H(153)-H(121)	2.312	H(141)-C(13)	2.035
H(142)-C(13)	2.035	C(15)-C(13)	2.524
H(151)-C(13)	2.687	H(152)-C(13)	2.727
H(132)-H(131)	1.568	C(14)-H(131)	2.039
H(142)-H(131)	2.326	C(14)-H(132)	2.039
H(141)-H(132)	2.324	H(142)-H(132)	2.272
C(15)-H(132)	2.531	H(151)-H(132)	2.355
H(142)-H(141)	1.568	H(152)-H(151)	1.568
H(153)-H(151)	1.568	H(153)-H(152)	1.568

Intermolecular:

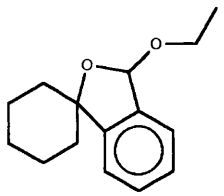
O(2)-N(1a)	2.874	H(101)-O(1b)	2.685
H(1)-O(2a)	1.986	H(71)-O(2c)	2.476

Key to symmetry operations relating
designated atoms to reference atoms
at (x,y,z):

(a) -x,-y,-z
(b) -1.0-x,-0.5+y,-0.5-z
(c) -1.0+x,0.5-y,-0.5+z

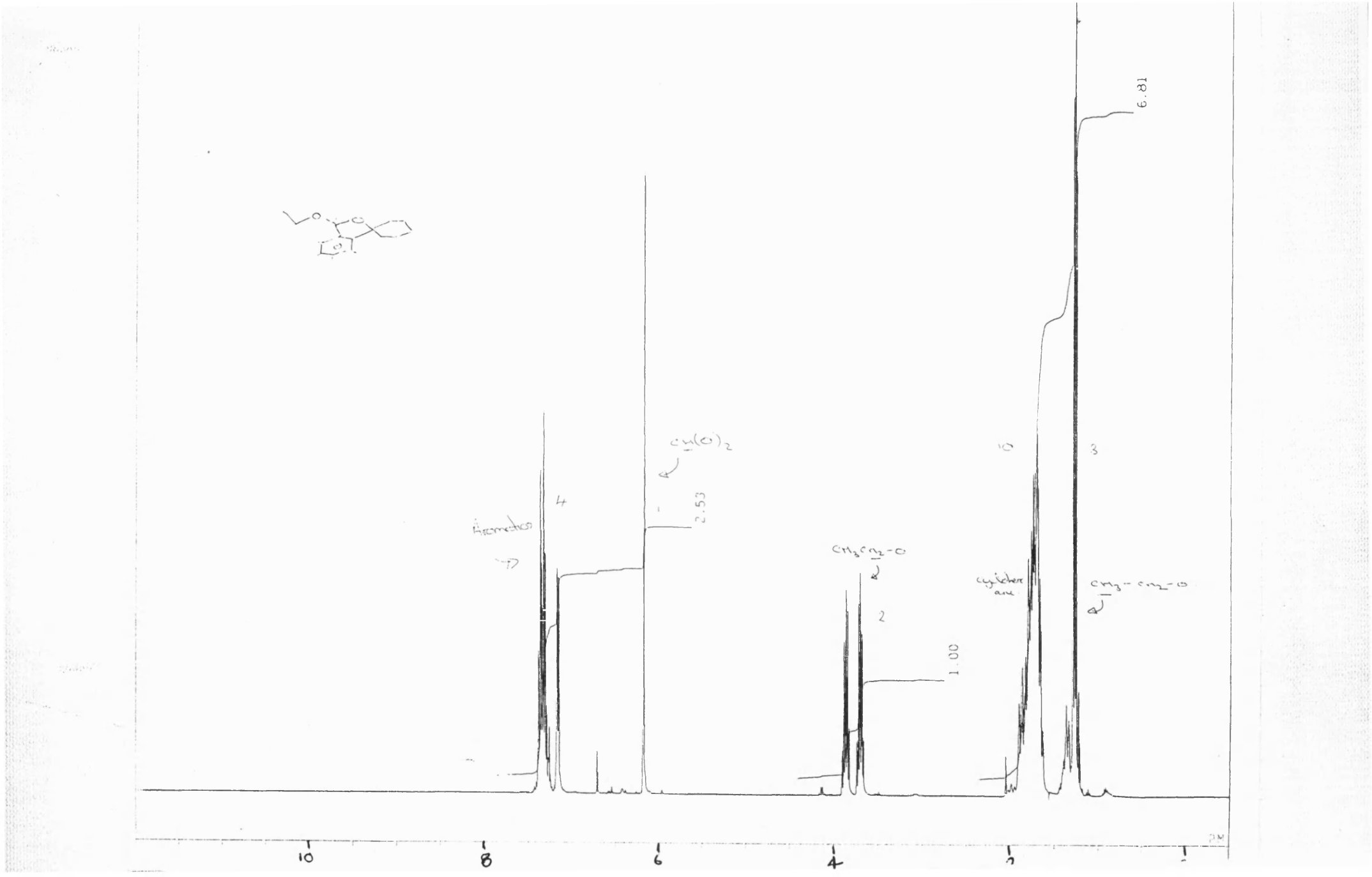
Appendix iii

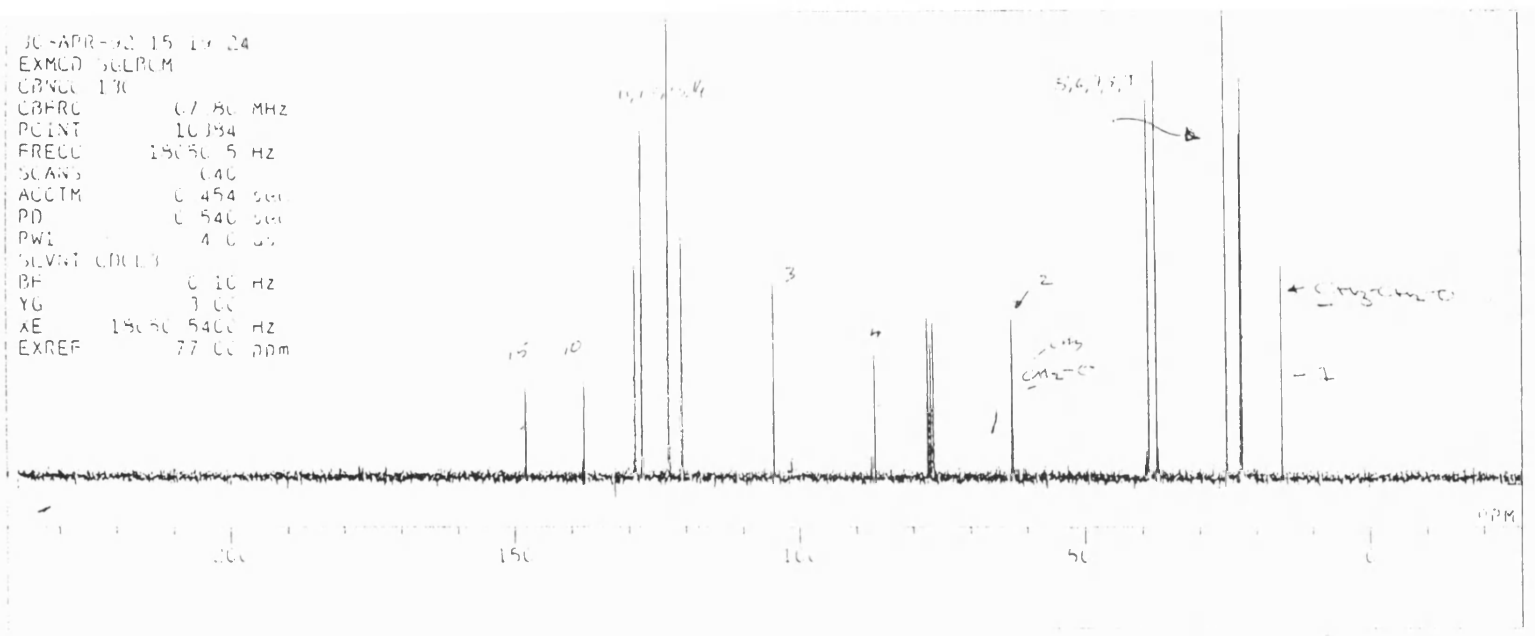
^{13}C, ^{1}H, 2D, NOESY and COSEY spectral data for selected compounds

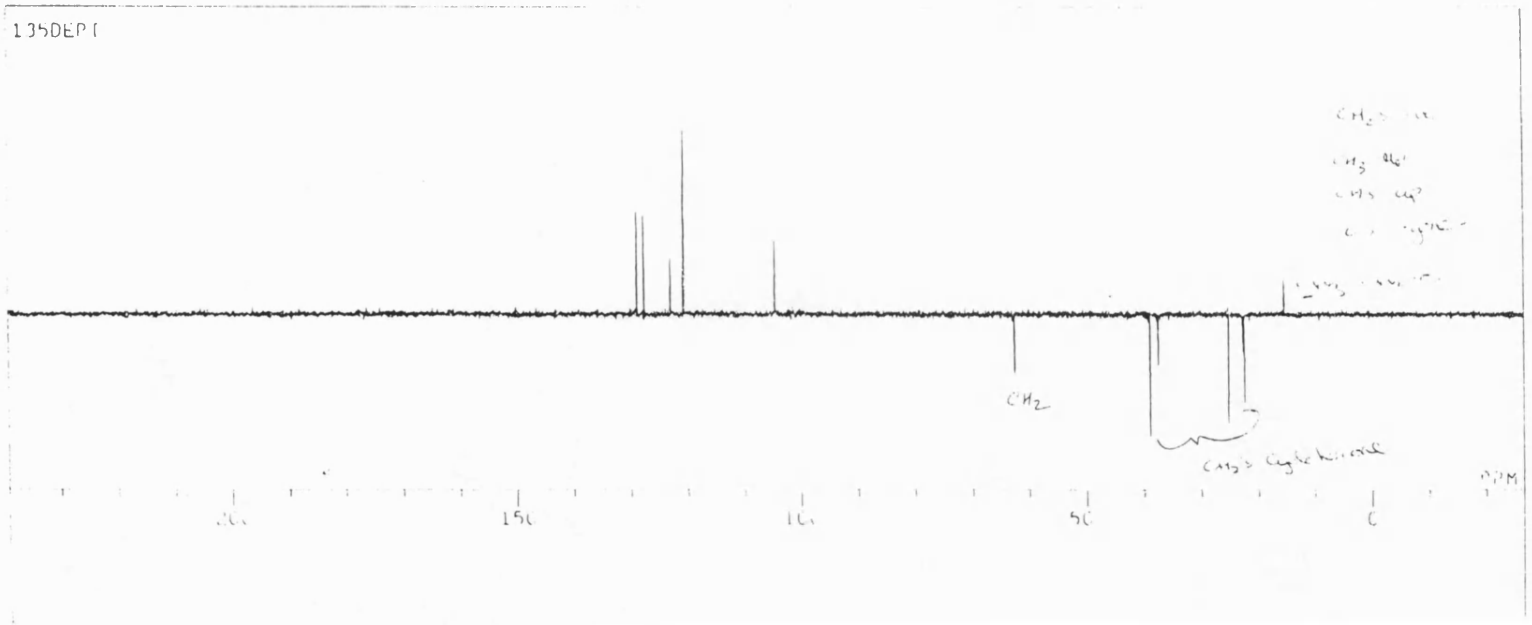


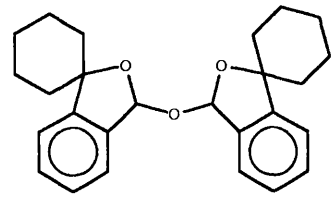
Compound 29

^{1}H, ^{13}C


6.81
3
10
4
2.53
1
2
1.00
aromatics
cyclohexane
10
8
6
4
2
1

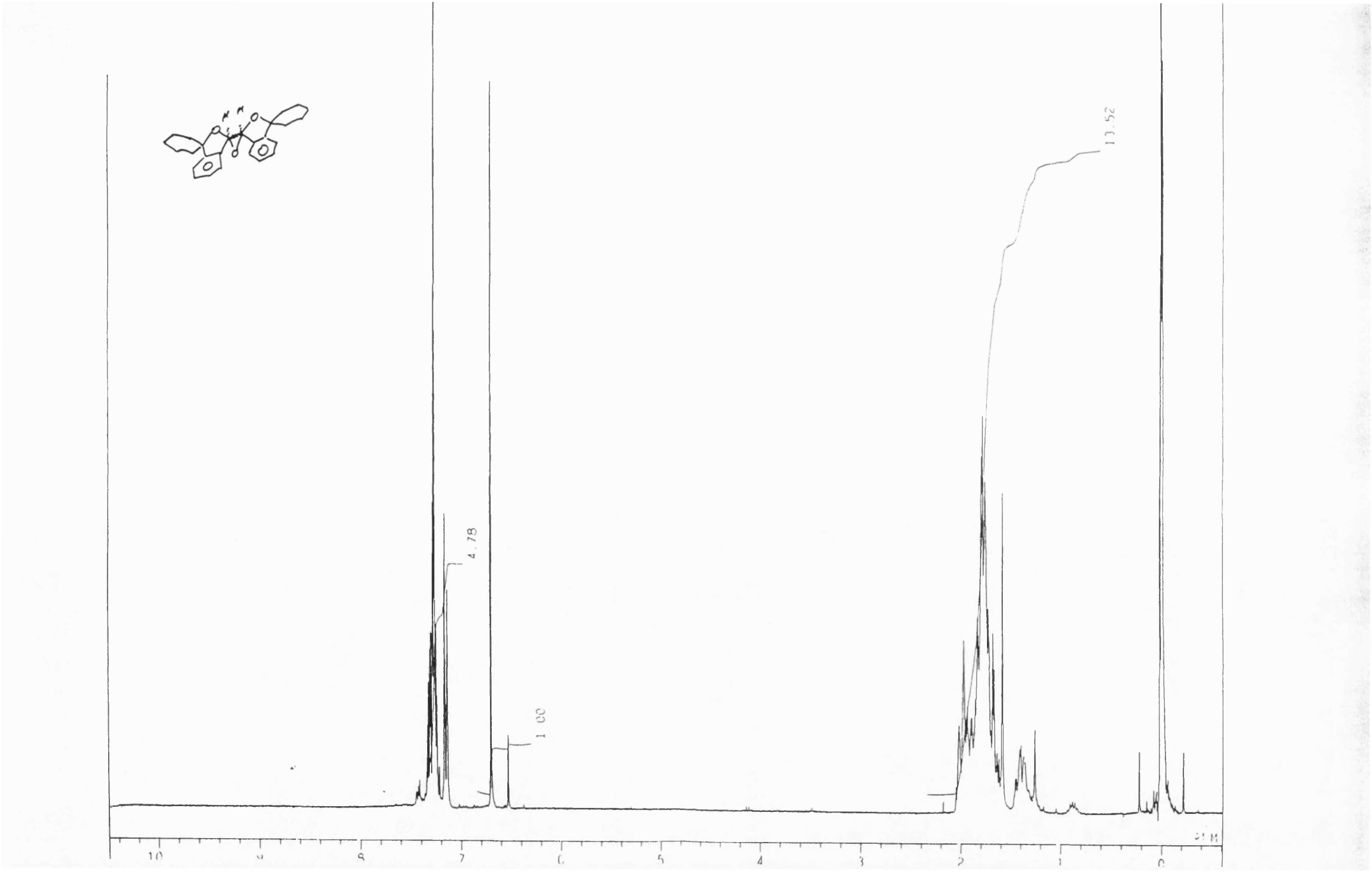

EXMOD SGLPROM
CBFRQ 67.80 MHz
POINT 16384
FREQU 15050.5 Hz
SCANS 640
ACQTM 0.454 sec
PD 0.540 sec
PW1 4.0 us
SOLVNT CDCL3
BF 0.10 Hz
YG 7.00
AE 15050.5400 Hz
EXREF 77.00 ppm
3
2
1
PPM
200
150
100
50
0

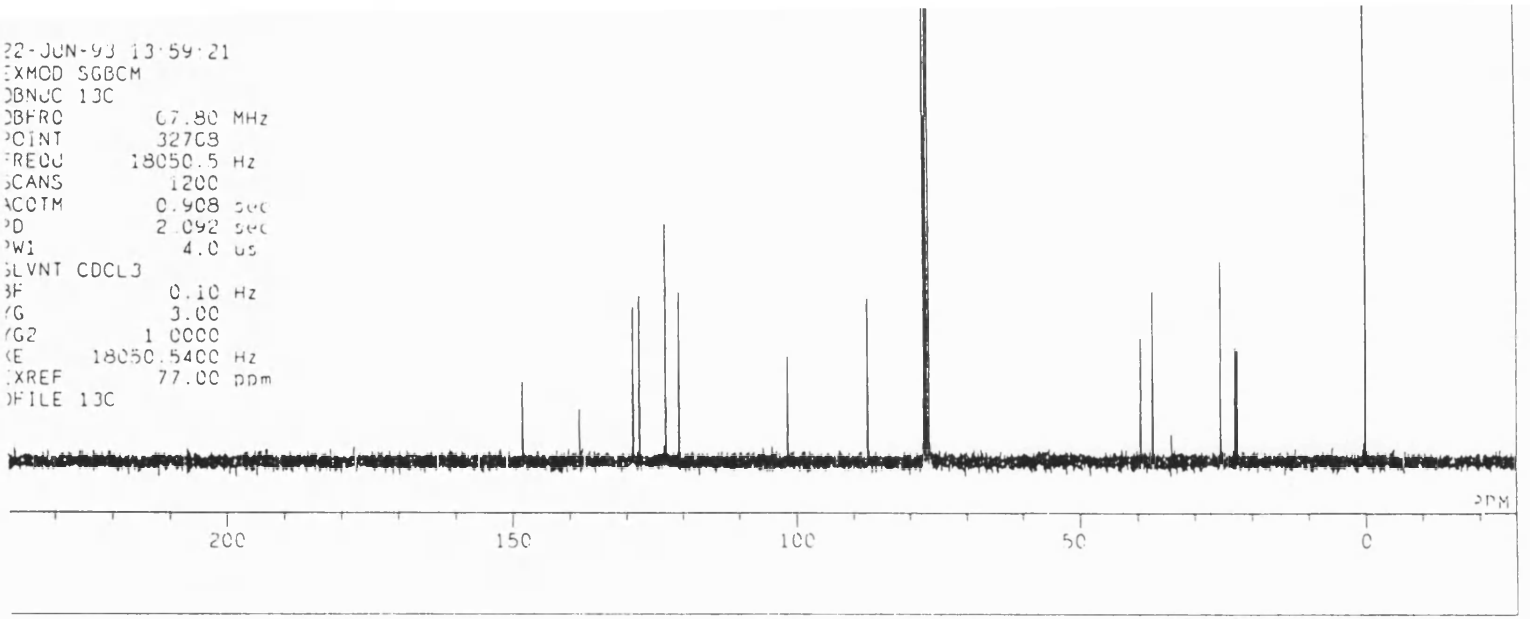

135DEPT
CH2
PPM
200
150
100
50
0

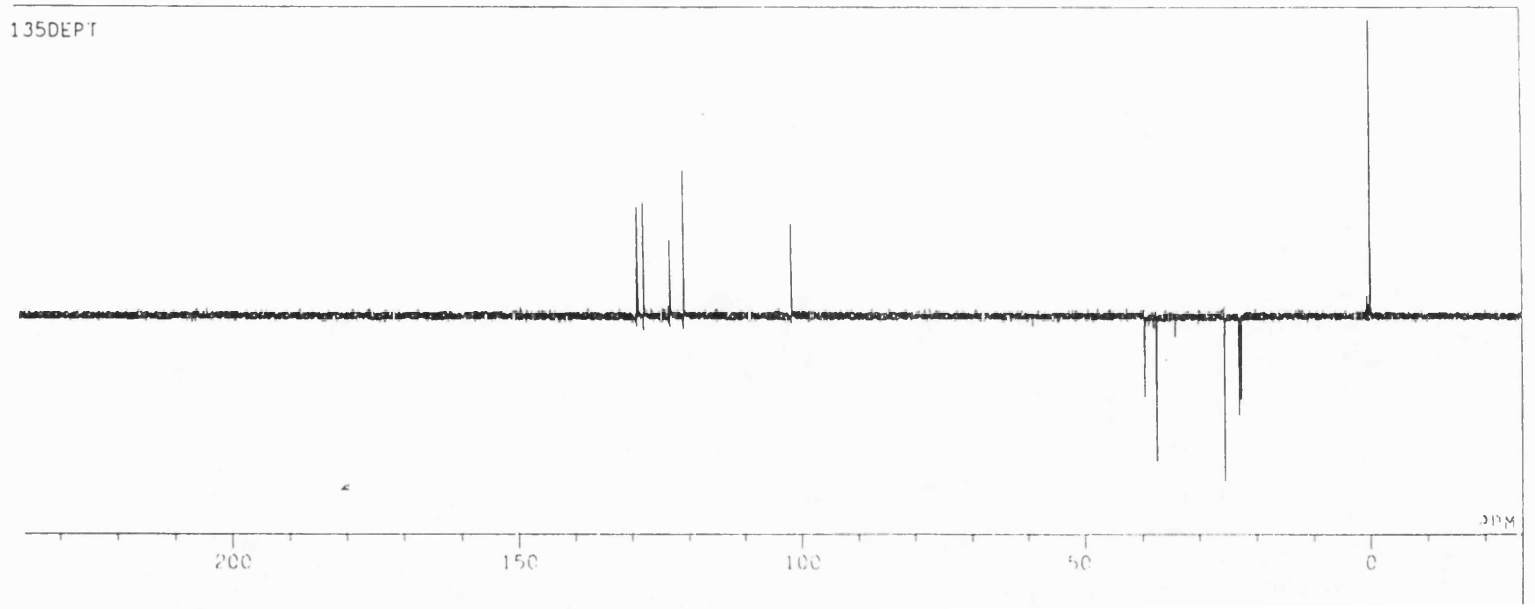


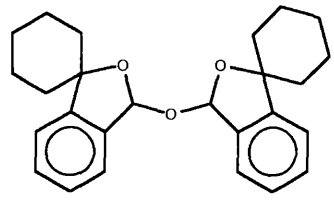
Compound 30A

^{1}H, ^{13}C


4.78
1.00
13.52
10
9
8
7
6
5
4
3
2
1
0


22-JUN-93 13:59:21
EXMOD SGBCM
OBNUC 13C
OBFRQ 67.80 MHz
POINT 32768
FREQU 18050.5 Hz
SCANS 1200
ACQTM 0.908 sec
PD 2.092 sec
PW1 4.0 us
SLVNT CDCL3
BF 0.10 Hz
FG 3.00
FG2 1.0000
SE 18050.5400 Hz
EXREF 77.00 ppm
OFILE 13C
PPM
200
150
100
50
0

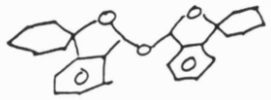

135DEPT
PPM
200
150
100
50
0

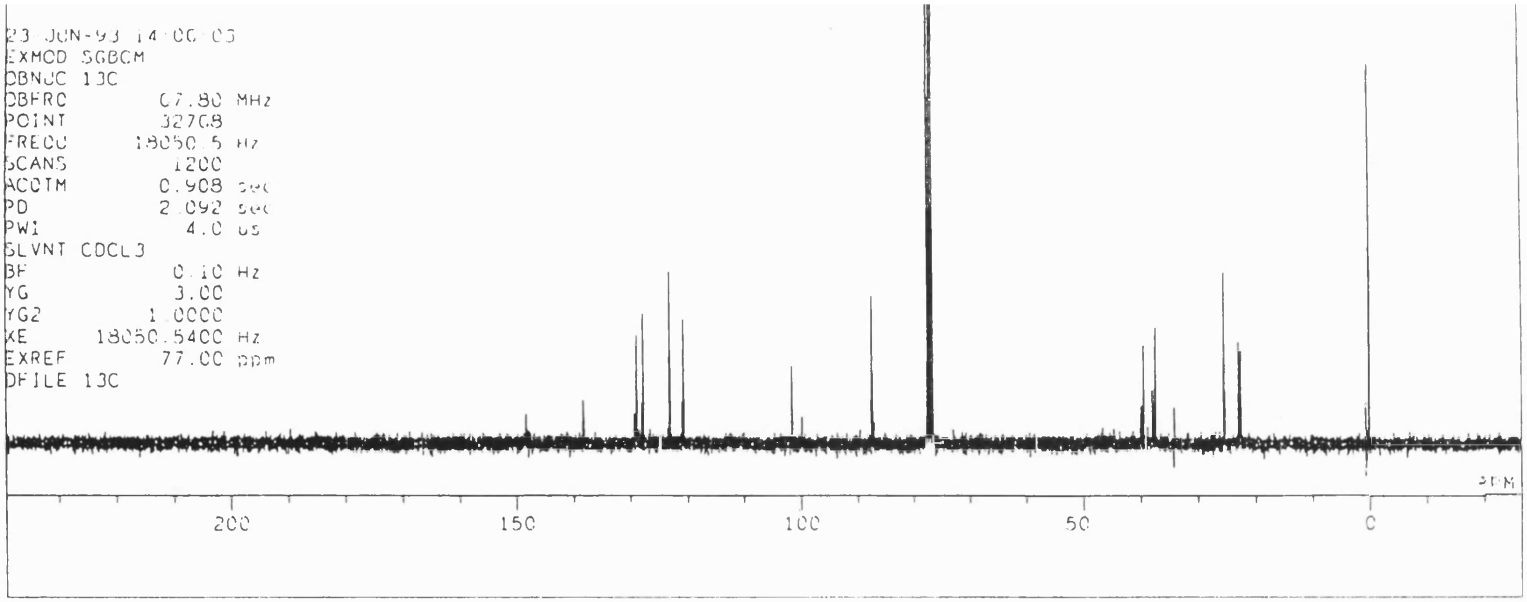


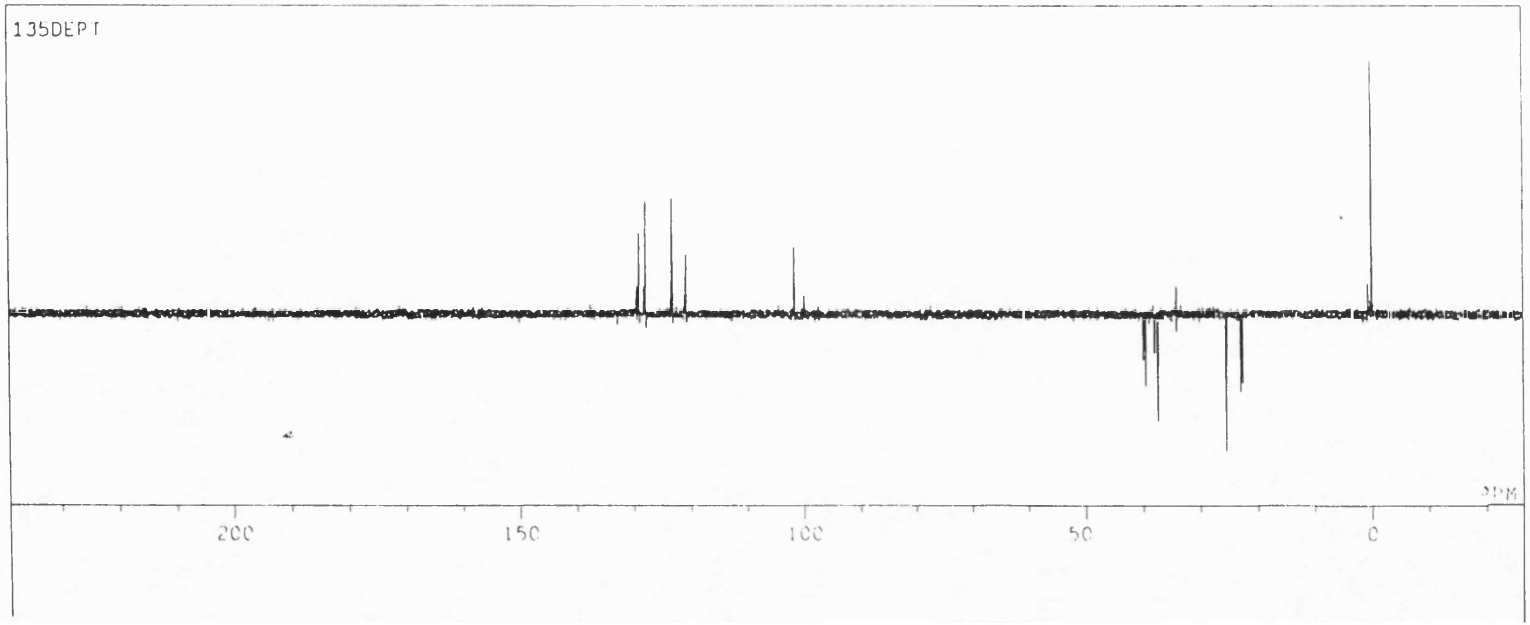
Compound 30B

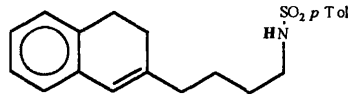
^{1}H, ^{13}C

AG15B



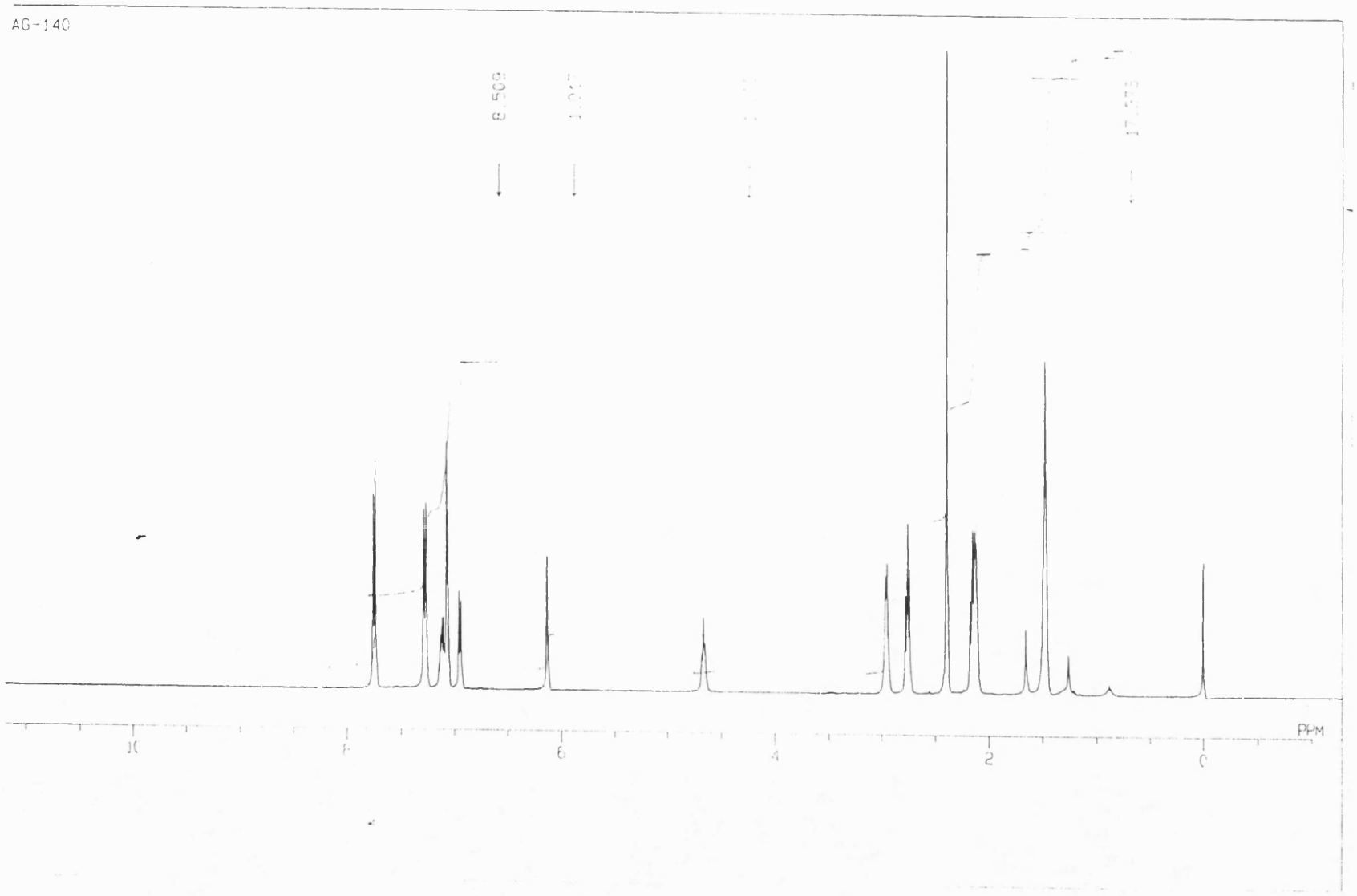

23 JUN-93 14:00:05
EXMOD SGBCM
OBNUC 13C
OBFRQ 67.80 MHz
POINT 32768
FREQU 18050.5 Hz
SCANS 1200
ACQTM 0.908 sec
PD 2.092 sec
PW1 4.0 us
SLVNT CDCL3
BF 0.10 Hz
YG 3.00
YG2 1.0000
XE 18050.5400 Hz
EXREF 77.00 ppm
DFILE 13C
PPM
200
150
100
50
0

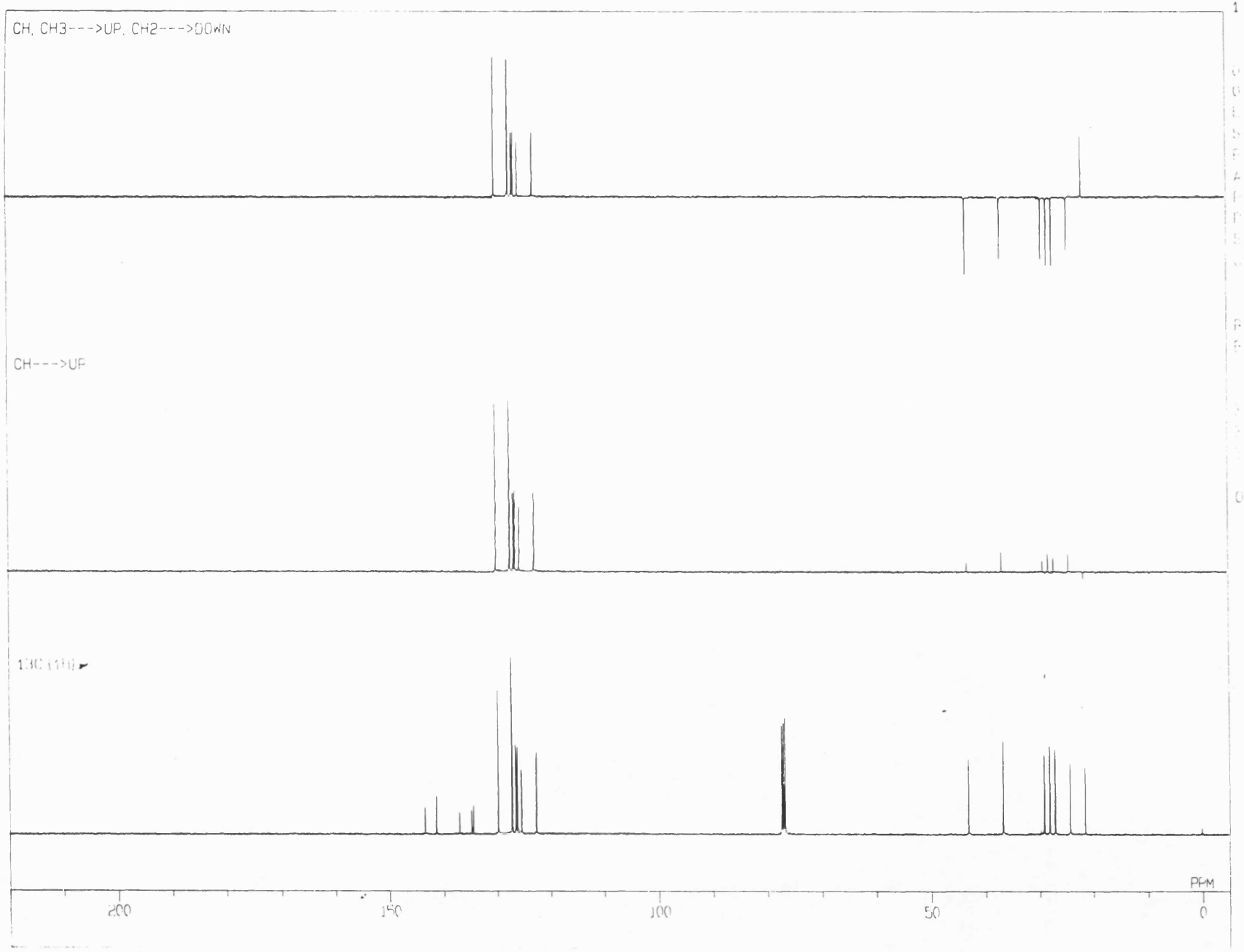

135DEPT
PPM
200
150
100
50
0

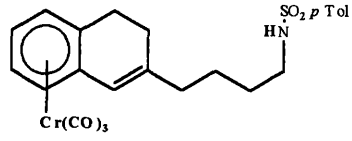


Compound 73

^{1}H, ^{13}C

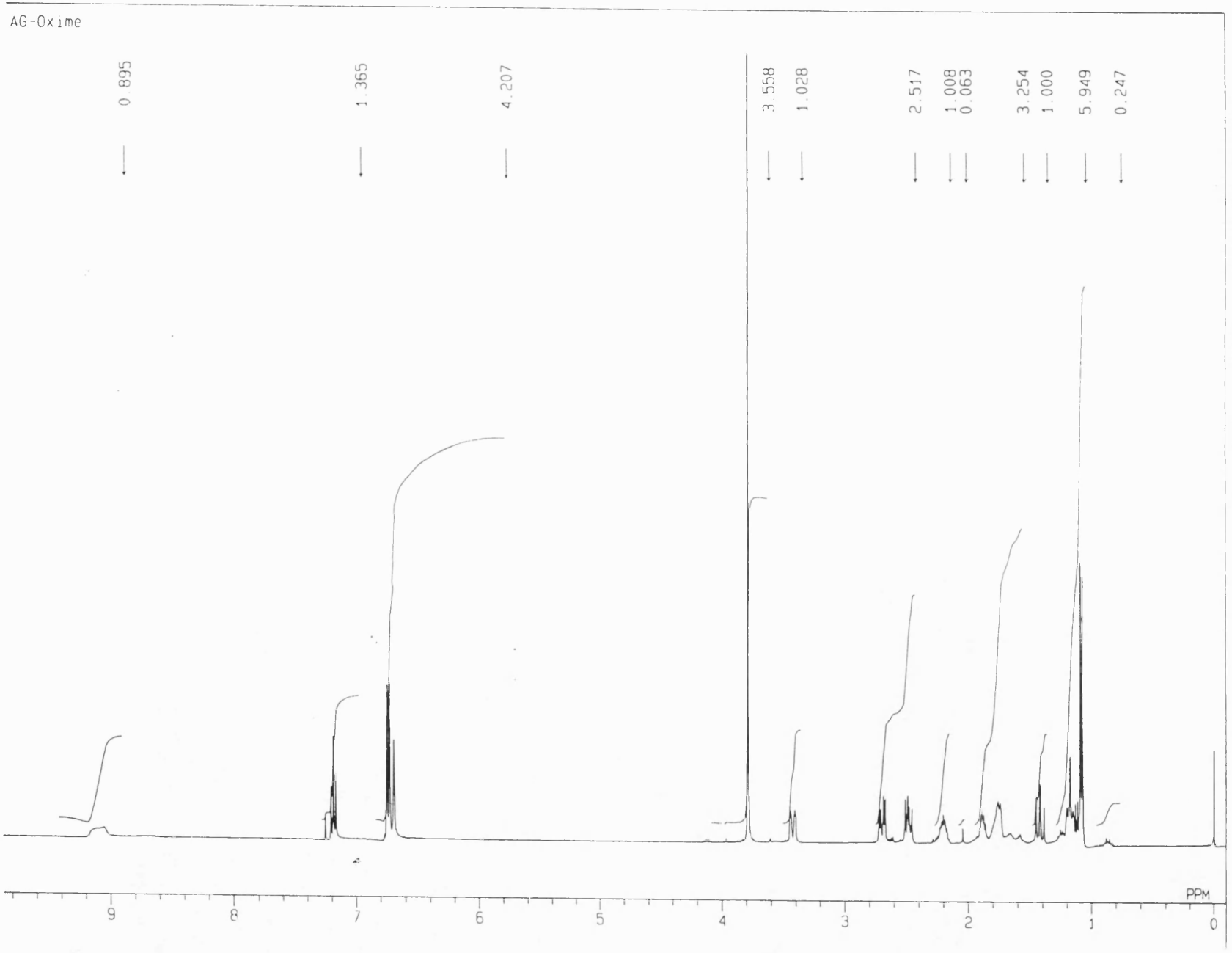

AG-140
8.508
1.327
17.778
PPM
8
6
4
2
0

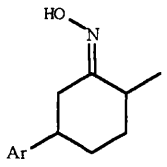

CH, CH3--->UP, CH2--->DOWN
CH--->UP
PPM
200
150
100
50
0



Compound 76

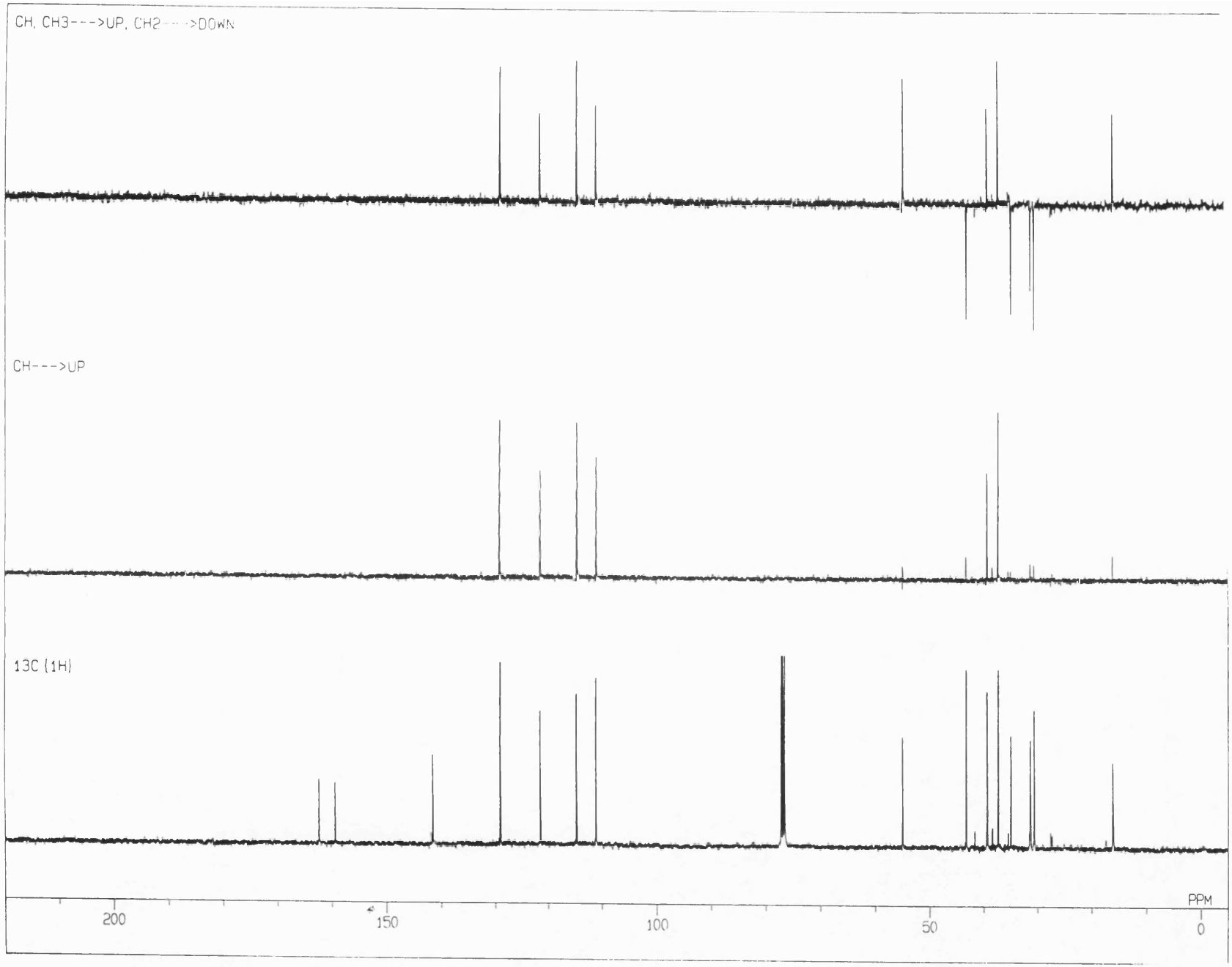
^{13}C

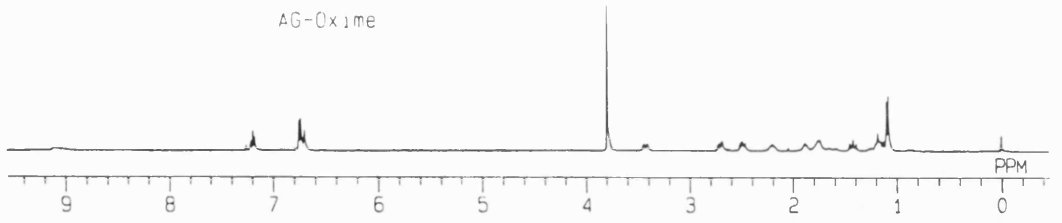

AG-Oxime
0.895
1.365
4.207
3.558
1.028
2.517
1.008
0.063
3.254
1.000
5.949
0.247
PPM
9
8
7
6
5
4
3
2
1
0

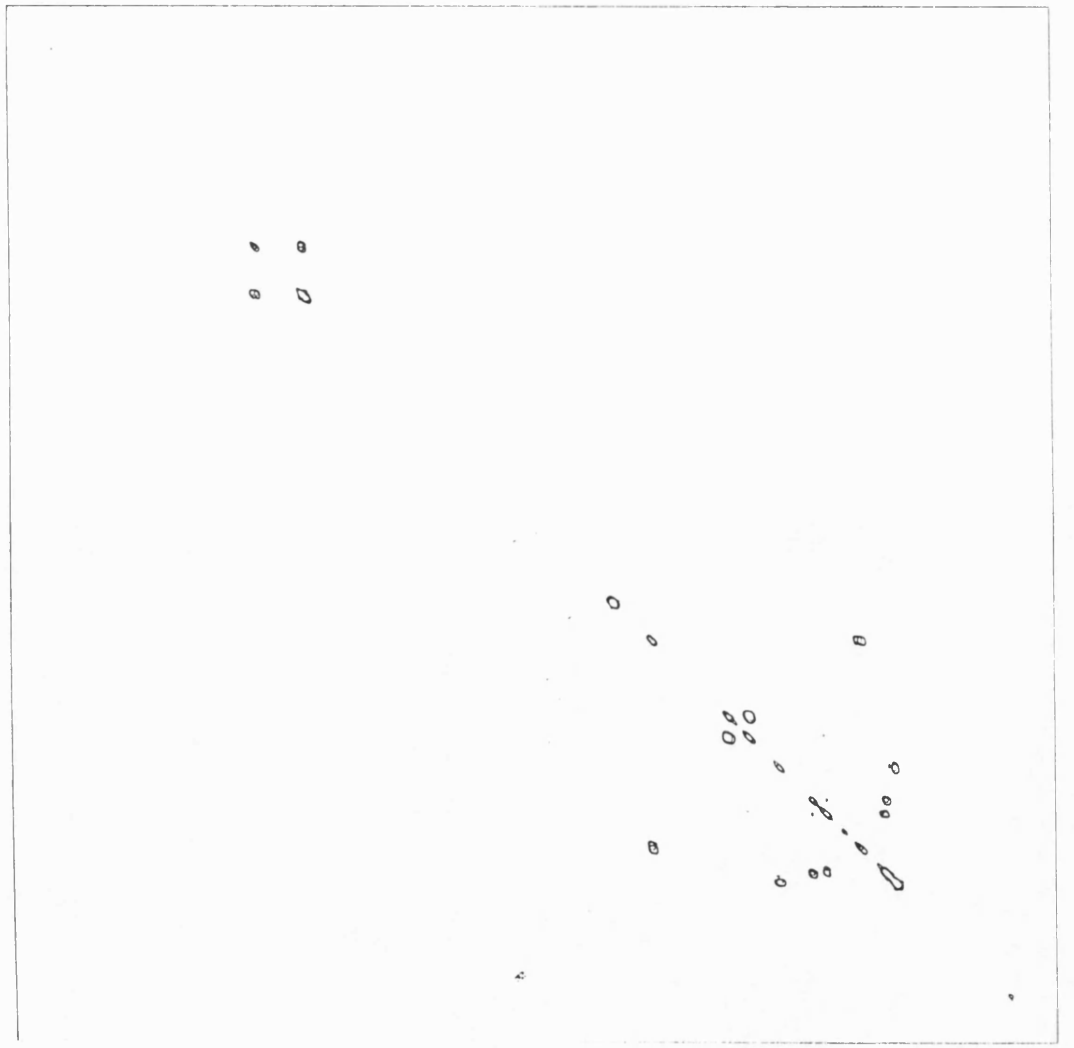


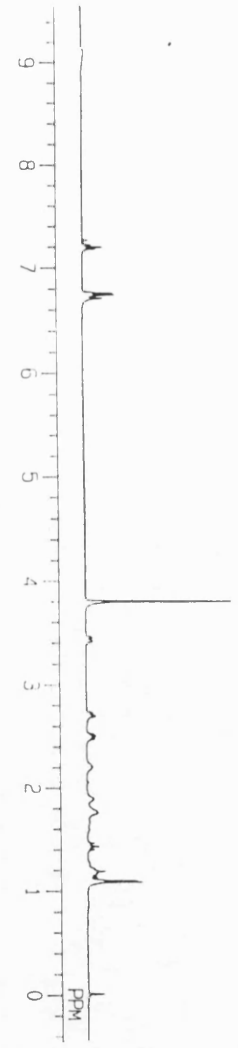
Compound 85

^{1}H, ^{13}C, ^{1}H-^{1}H, COSEY, ^{13}C-^{1}H

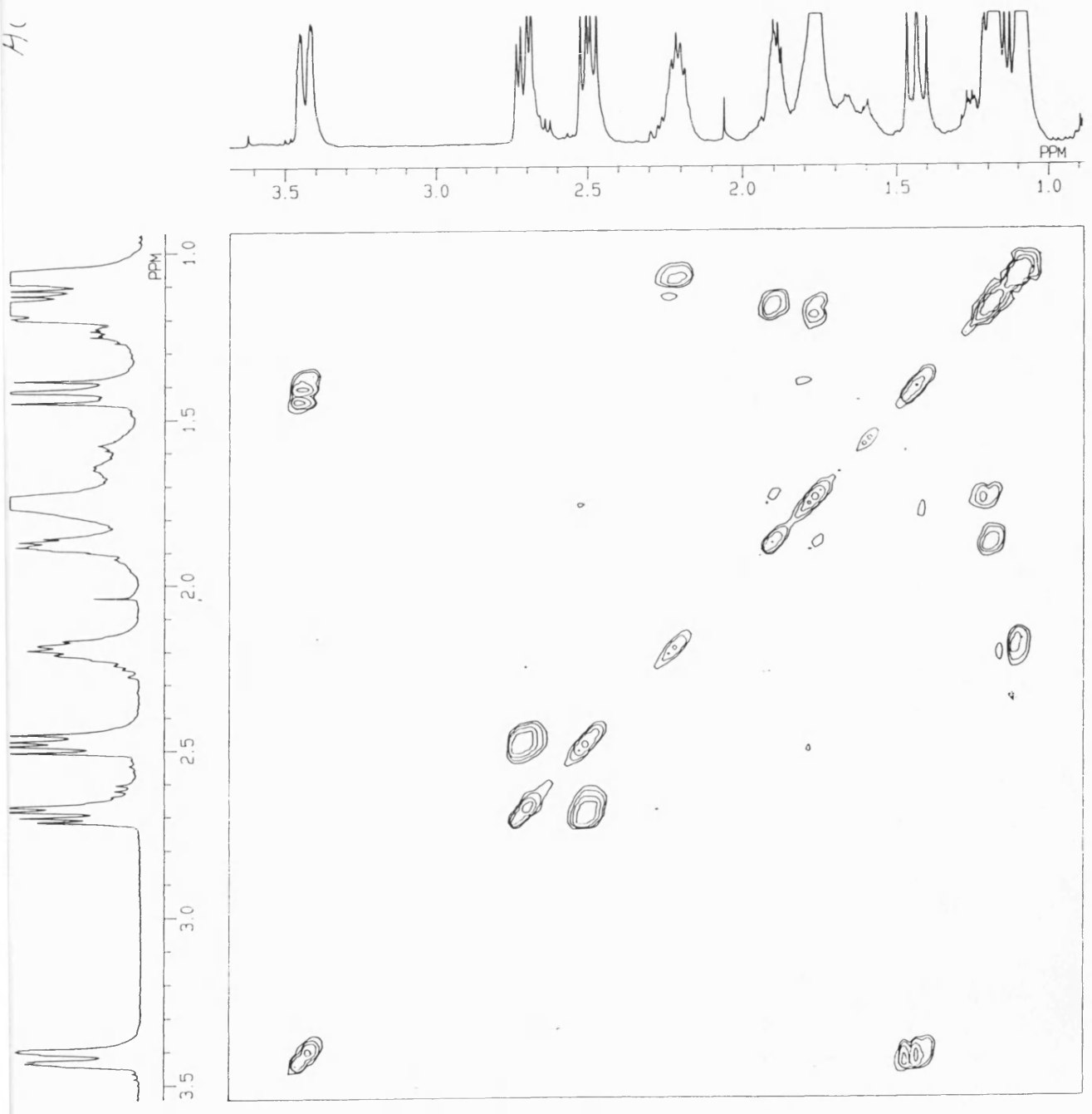

CH, CH3--->UP, CH2---->DOWN
CH--->UP
13C {1H}
200
150
100
50
0
PPM

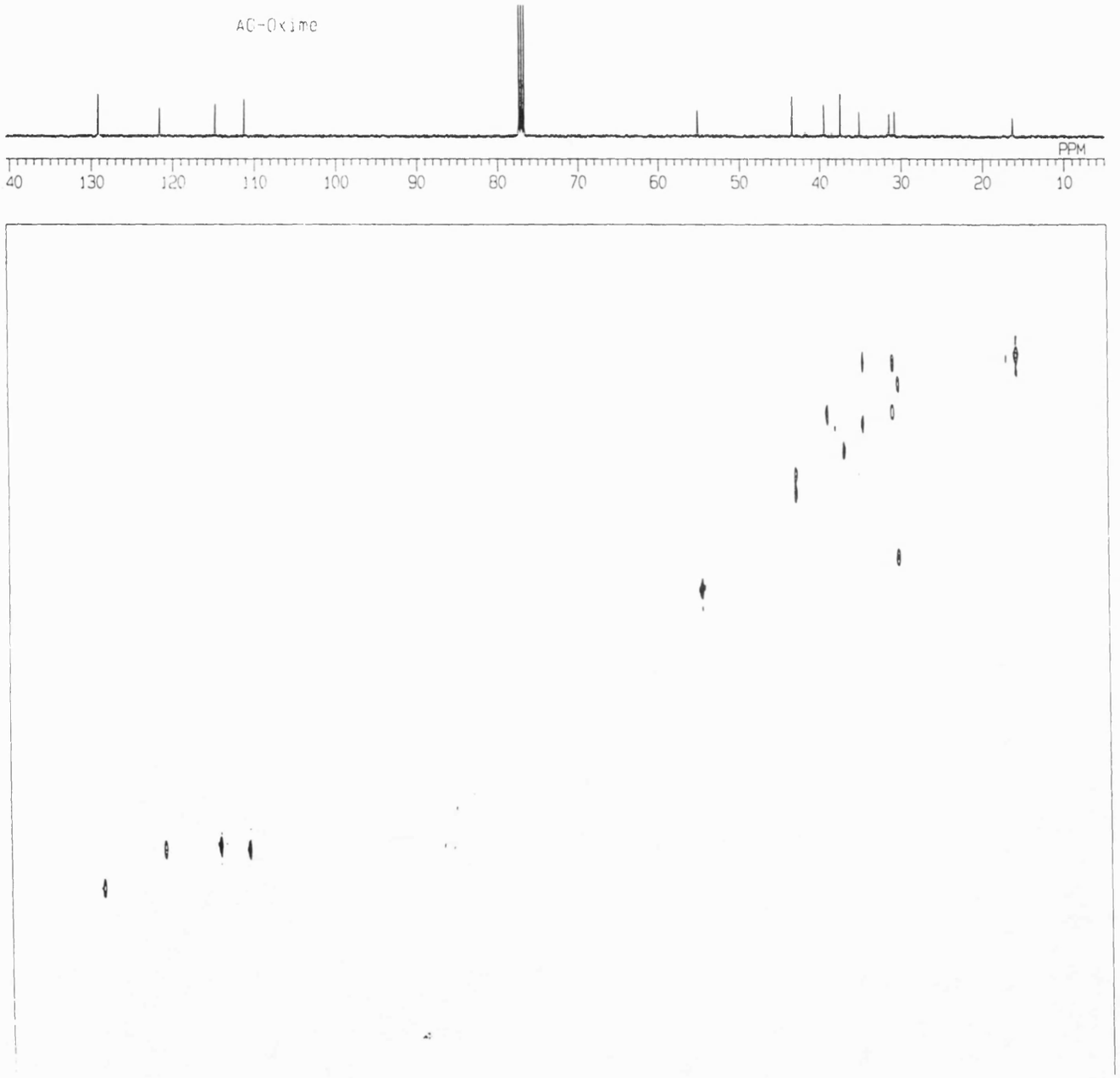

AG-Oxime
PPM
9
8
7
6
5
4
3
2
1
0



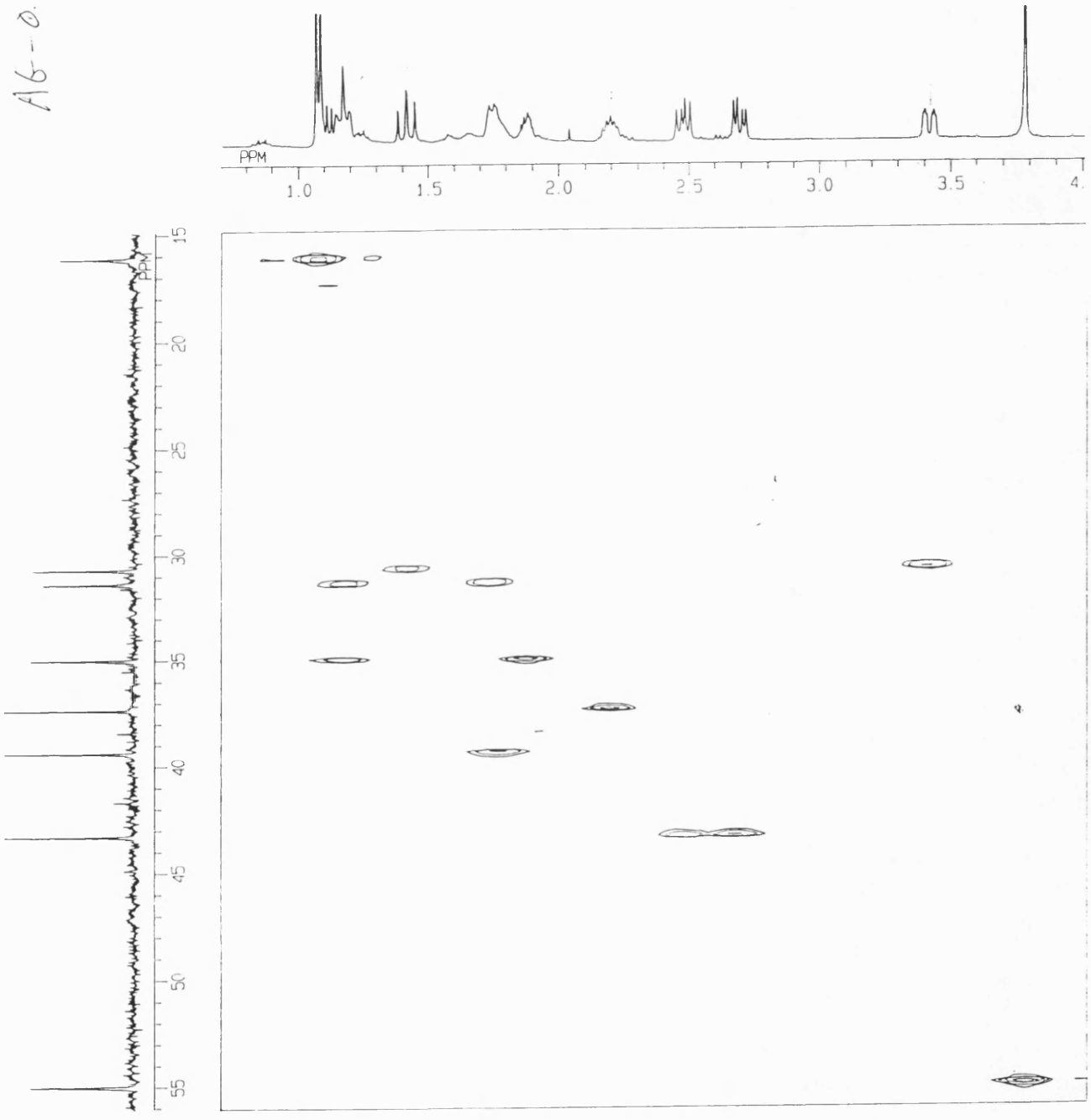

PPM
0
1
2
3
4
5
6
7
8
9

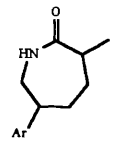
PPM
0
1
2
3
4
5
6
7
8
9
Wdd
0
1
2
3
4
5
6
7
8
9


PPM
3.5
3.0
2.5
2.0
1.5
1.0
PPM
1.0
1.5
2.0
2.5
3.0
3.5


AC-Oxime
PPM
40
130
120
110
100
90
80
70
60
50
40
30
20
10
PPM
0
1
2
3
4
5
6
7
8
9

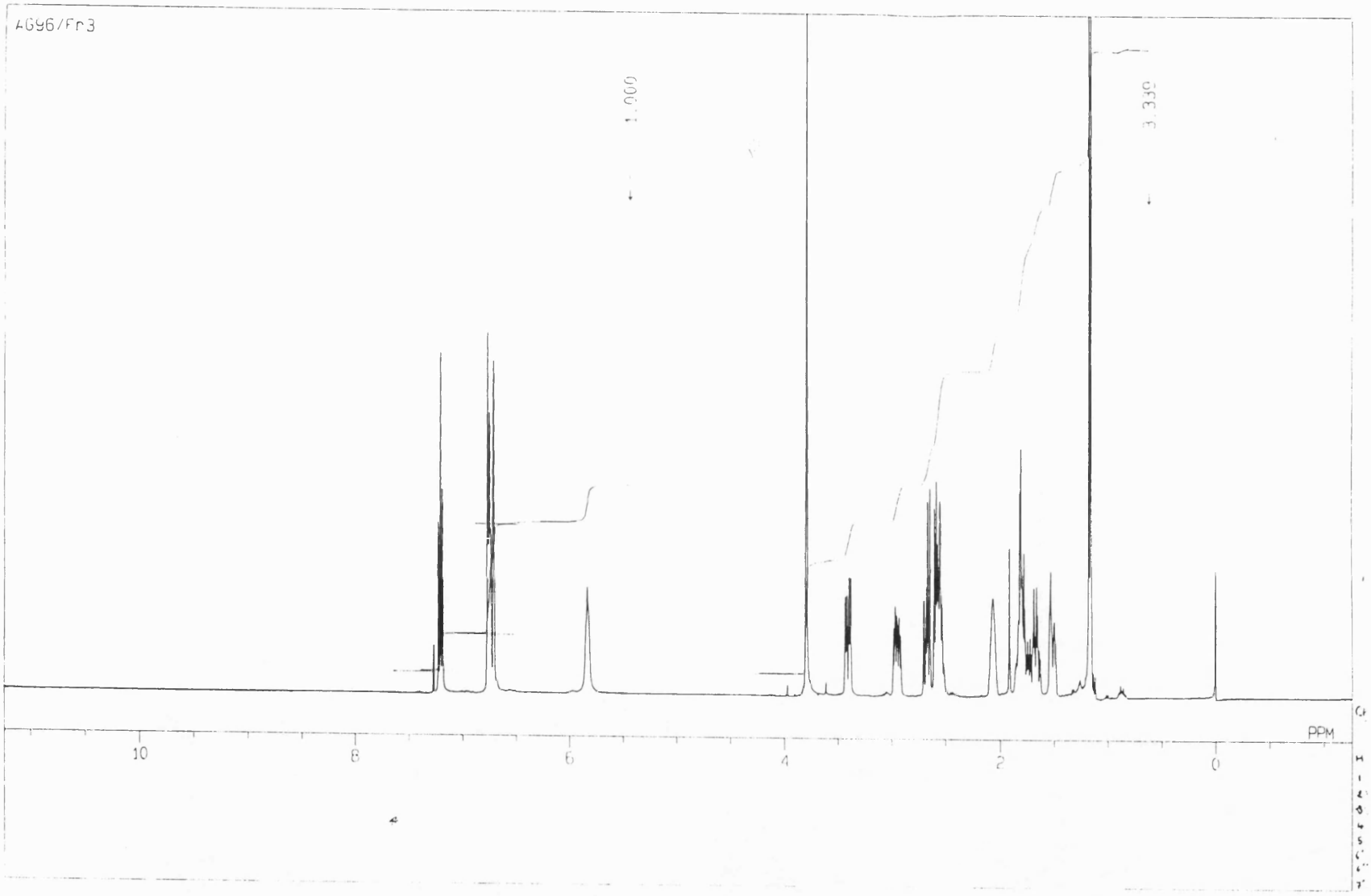
A16-0.

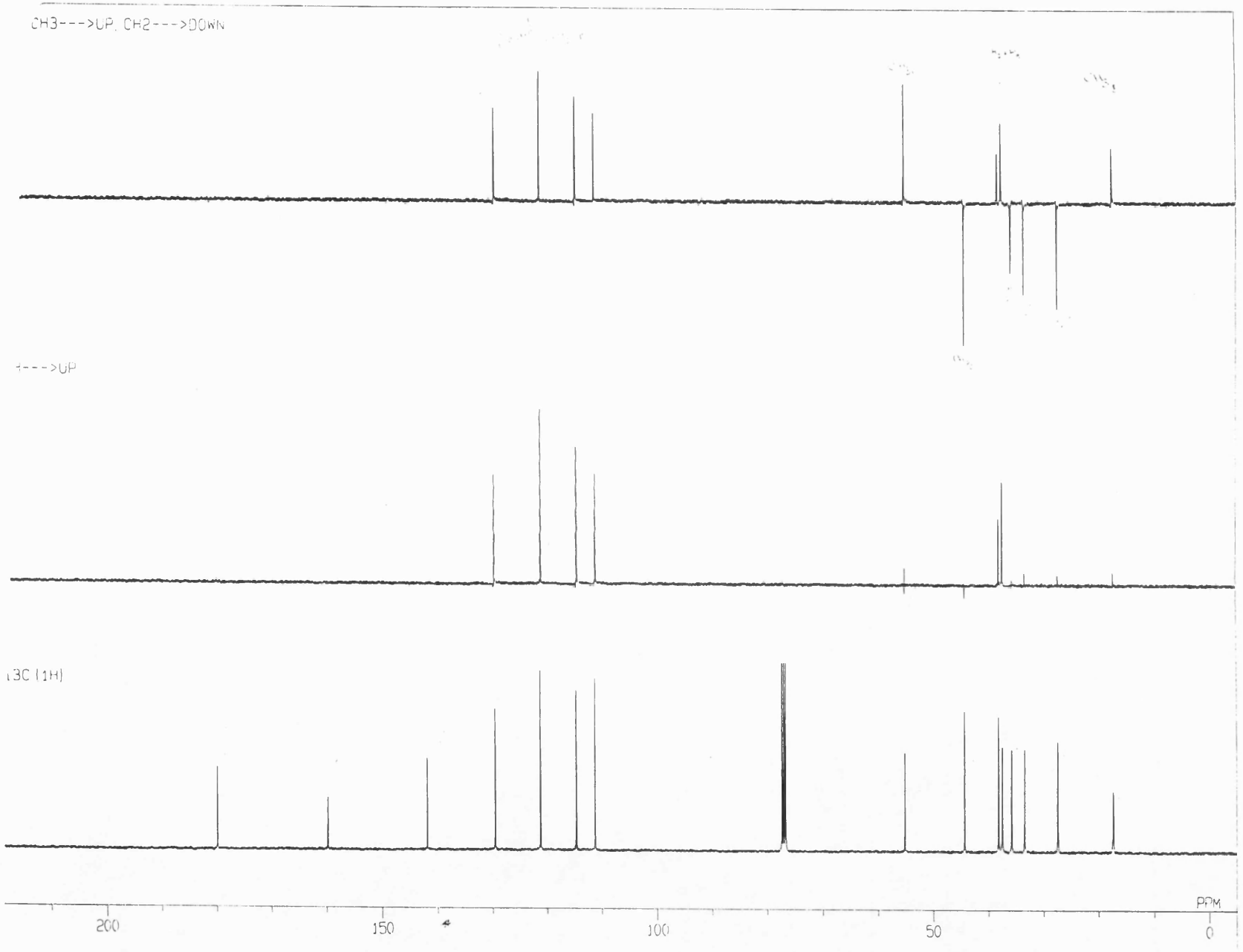


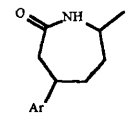


Compound 86

^{1}H, ^{13}C

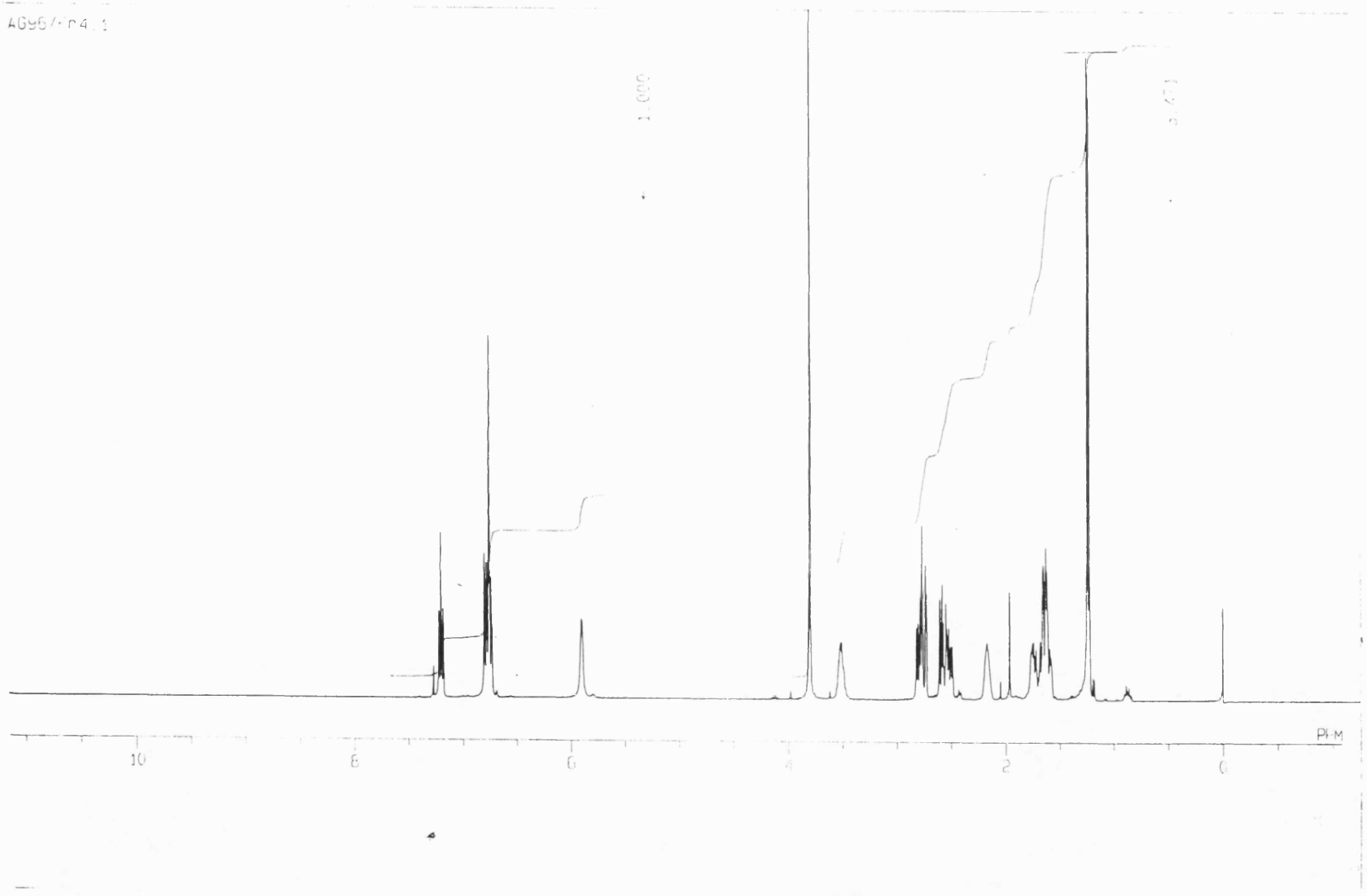

AG96/Fr3
1.000
3.339
PPM
10
8
6
4
2
0

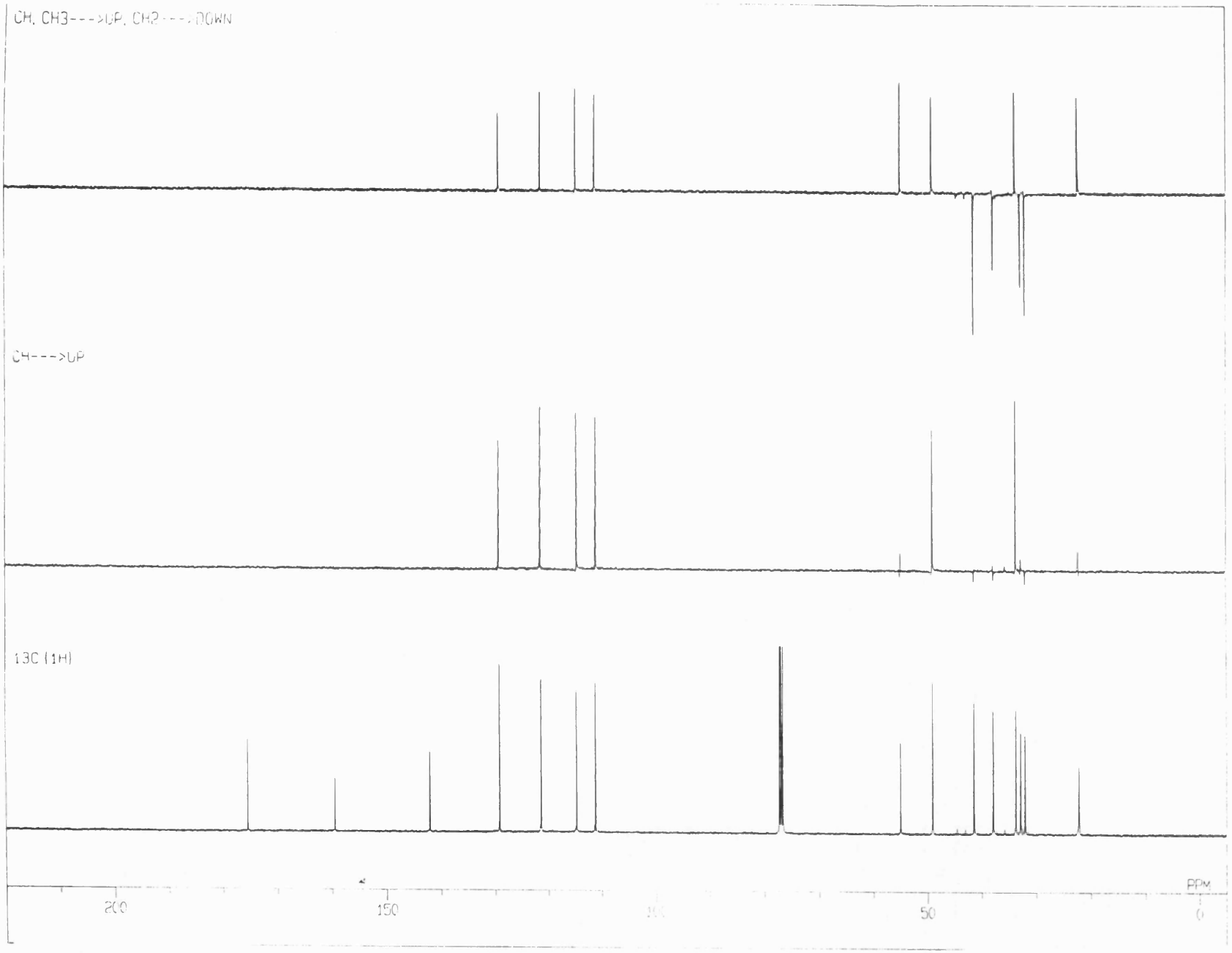

CH3--->UP, CH2--->DOWN
---->UP
13C {1H}
200
150
100
50
0
PPM

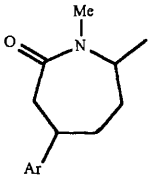


Compound 87

1H, 13C


PPM
10
8
6
4
2
0

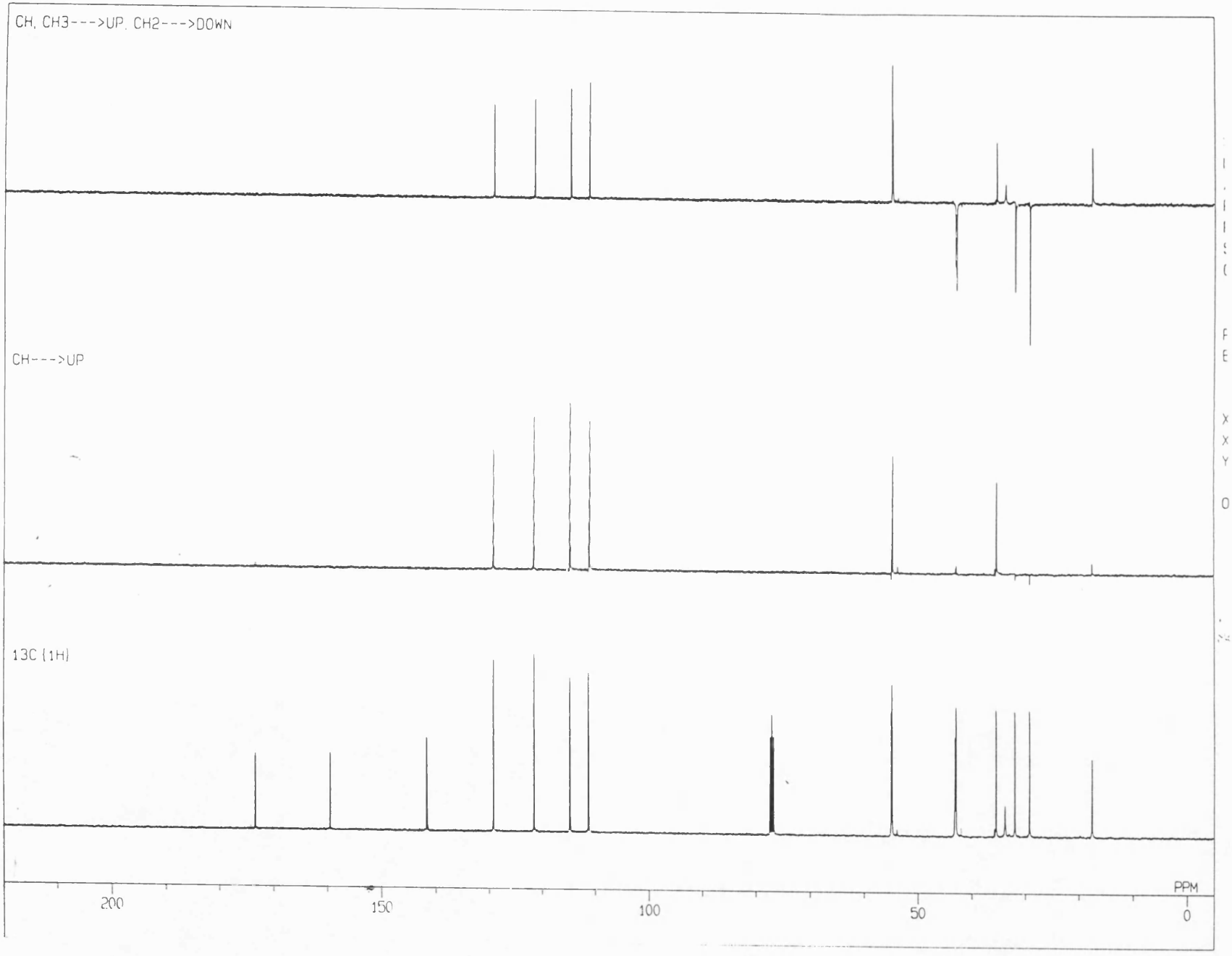

CH, CH3--->UP, CH2--->DOWN
C4--->UP
13C (1H)
200
150
50
0
PPM

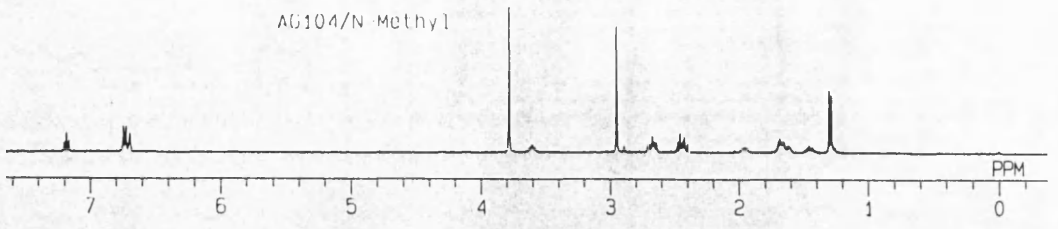


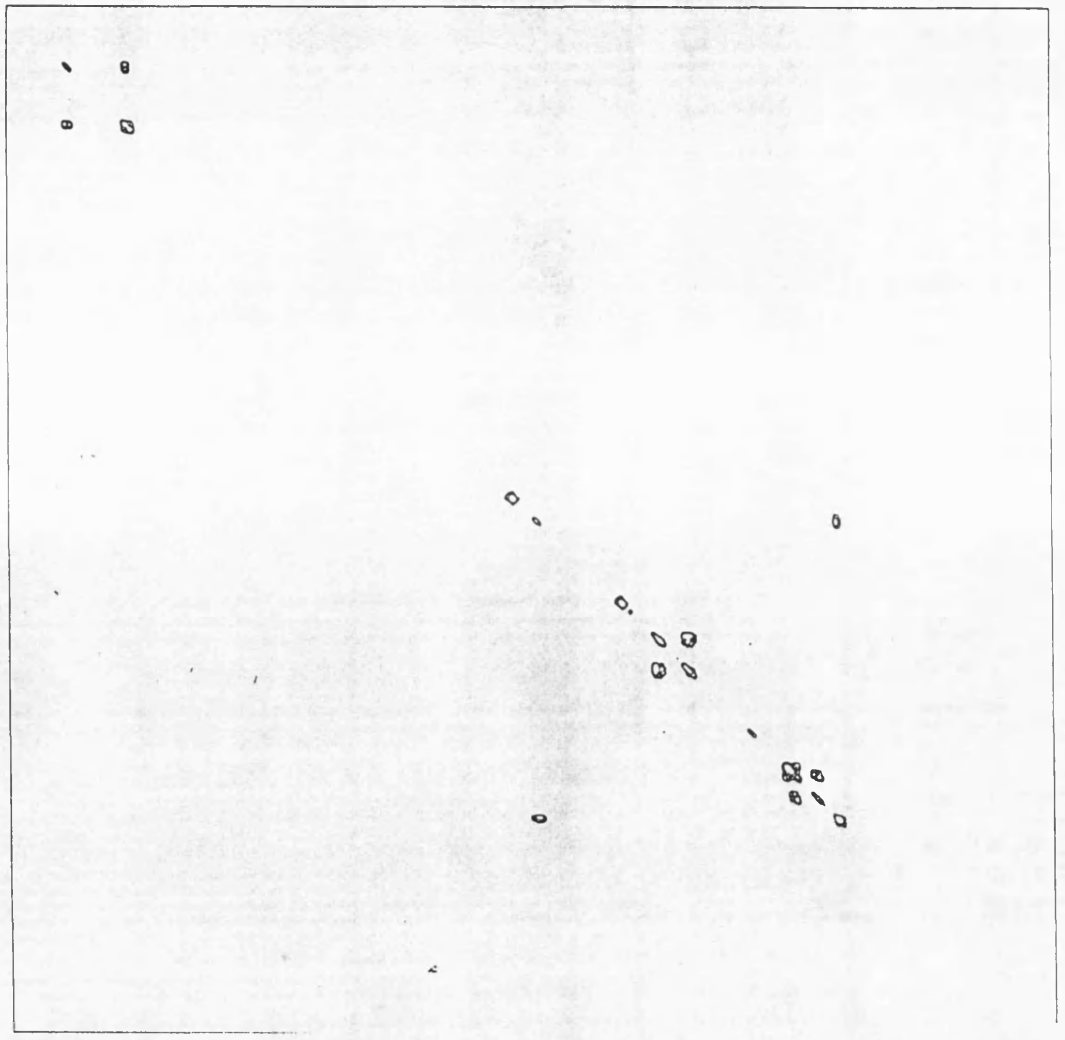
Compound 88

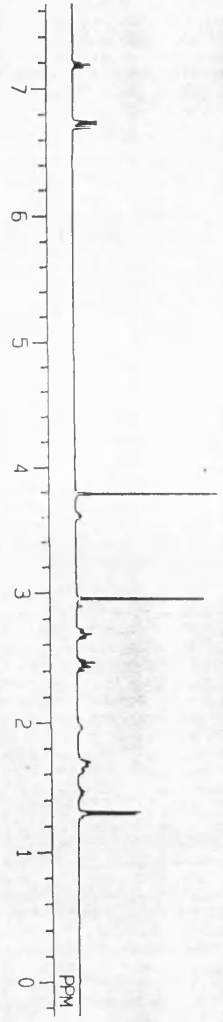
^{1}H, ^{13}C, ^{1}H-^{1}H COSEY

AG104/N-Methyl
7.713
24.515
0.096
32.339
0.068
54.785
8.326
23.588
34.929
1.000
PPM
0
1
2
3
4
5
6
7
8
9

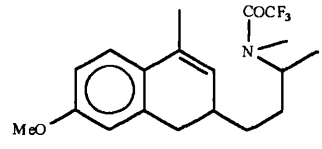

CH, CH3--->UP, CH2--->DOWN
CH--->UP
13C {1H}
200
150
100
50
0
PPM


AG104/N Methyl
PPM
7
6
5
4
3
2
1
0



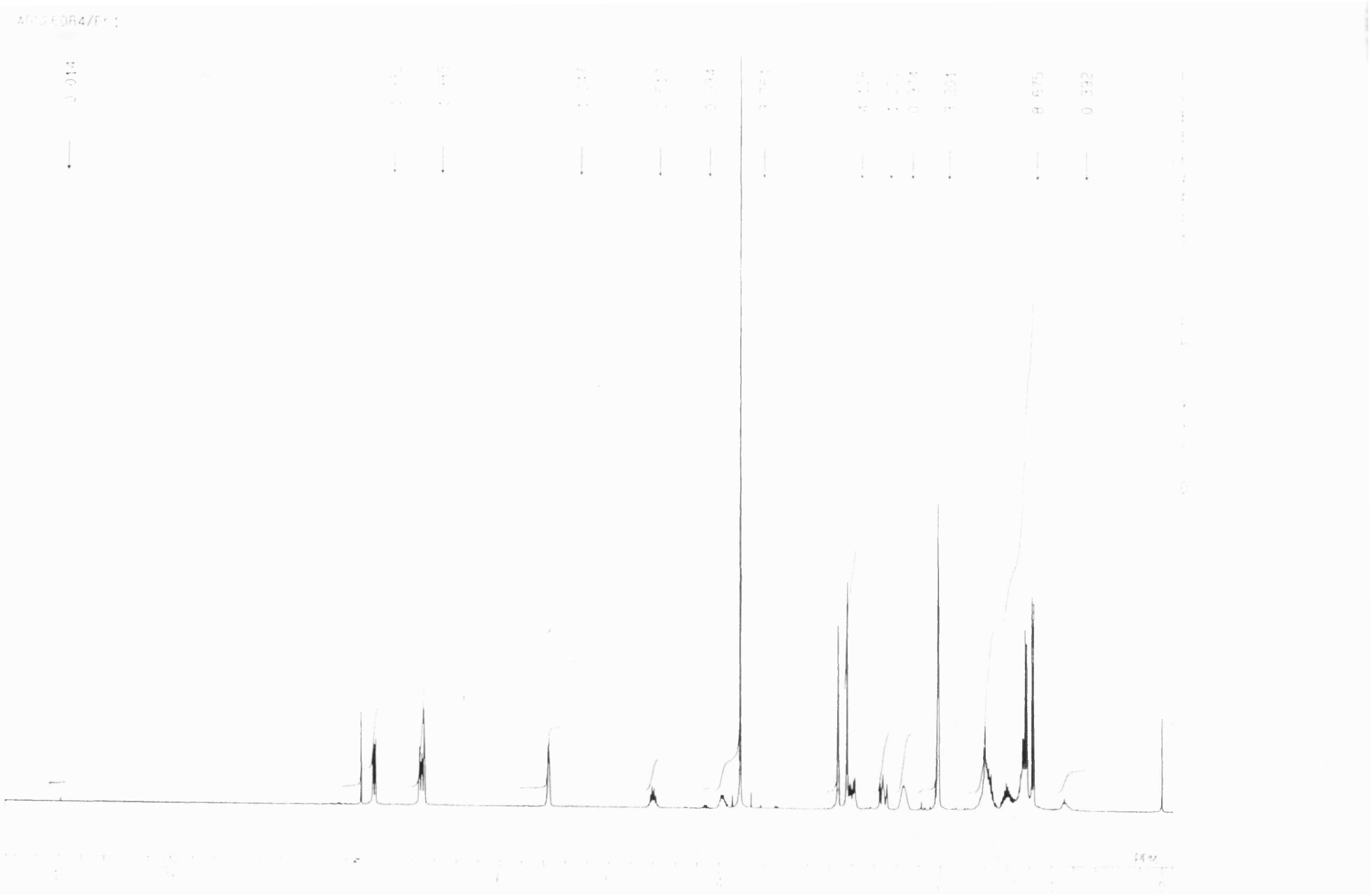

7
6
5
4
3
2
1
0
PPM

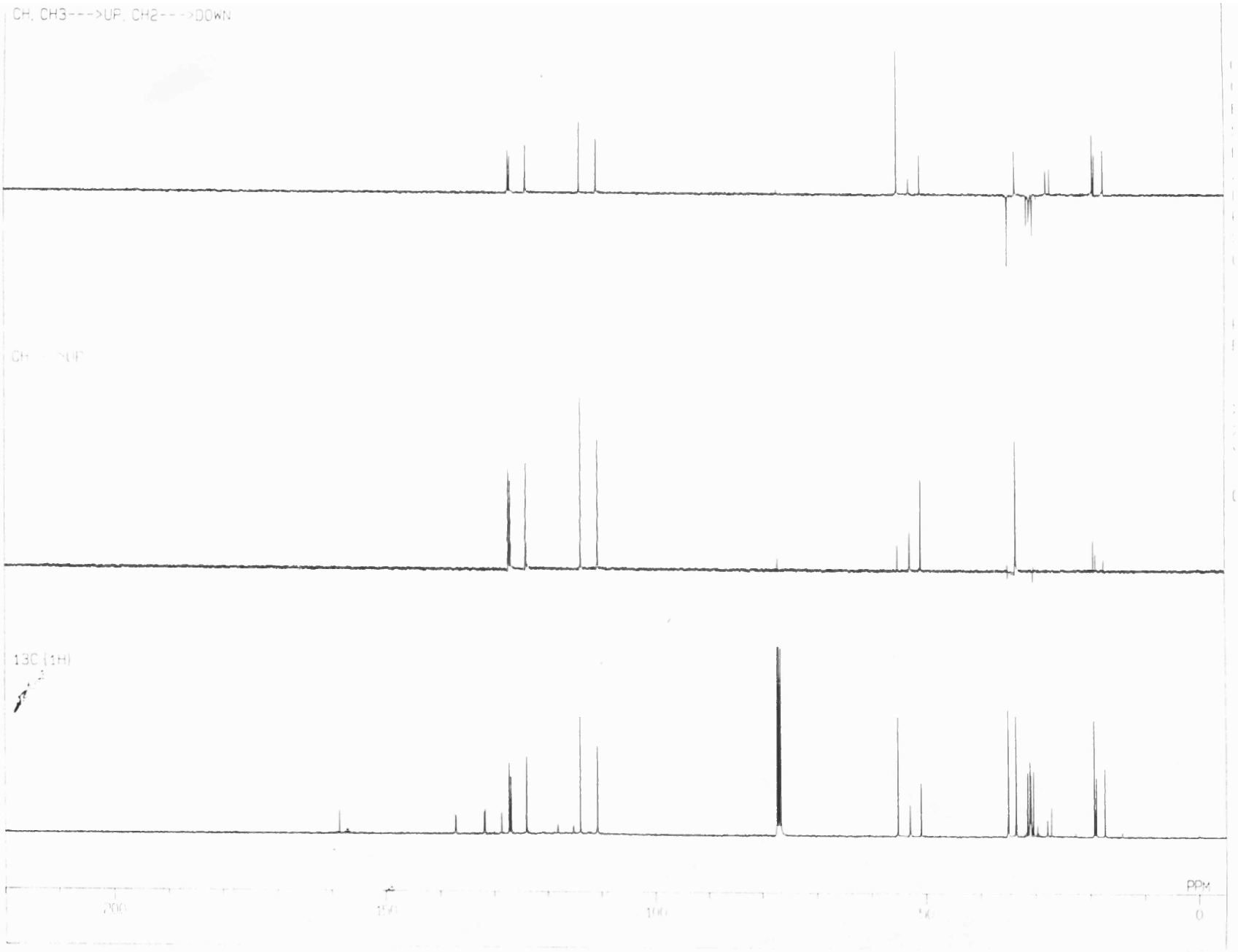
PPM
1.5
2.0
2.5
3.5
Hz



Compound 91

1H, 13C




CH, CH3--->UP, CH2--->DOWN
13C {1H}
PPM
200
150
100
50
0